

**METHAMPHETAMINE DEPENDENCE
IN MALAYSIA:
PSYCHIATRIC CO-MORBIDITY AND
SUICIDALITY, METHAMPHETAMINE INDUCED
PSYCHOSIS, GENETIC POLYMORPHISMS AND
EFFICACY OF ARIPIPRAZOLE IN THE
TREATMENT OF METHAMPHETAMINE
DEPENDENCE**

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**FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR**

JUNE 2011

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**THESIS SUBMITTED IN FULFILMENT
OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY**

**FACULTY OF MEDICINE
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KUALA LUMPUR**

JUNE 2011

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Title of Project Paper/Research Report/Dissertation/Thesis:

Methamphetamine Dependence in Malaysia: Psychiatric Co-Morbidity and Suicidality, Methamphetamine Induced Psychosis, Genetic Polymorphisms and Efficacy of Aripiprazole in the Treatment of Methamphetamine Dependence.

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Acknowledgements

In the name of Allah the Most Gracious and Merciful.

I am truly indebted to everyone who has helped me in completing this project. First and foremost, I would like to express my utmost gratitude to my supervisor, Professor Dr. Mohd Hussain Habil for his beneficial guidance, invaluable advice and commitments throughout this study. It was his trust and patience that assist me in overcoming the challenges along the way. An equal note of gratitude to my co-supervisor, Professor Dr. Mustafa Mohd Ali whom I am truly indebted for his guidance and assistance.

At the same time, I will like to express sincere appreciation and gratitude to Professor Zahurin Mohammed and Mr Shim Maw Shin from Pharmacogenomics Laboratory, Department of Pharmacology for their precious assistances and comments in the pharmacogenomic sections of my study. I would like to take this opportunity to thank the following respective parties, Associate Professor Dr. Jesjeet Singh Gill, Dr. Ng Chong Guan, Dr. Rusdi Abdul Rashid from Department of Psychological Medicine, Dr. Amer Siddiq Amer Nordin whom currently serving at National Addiction Centre, University of Otago, New Zealand, Miss Yamunah Devi Apalasamy and Miss Devika Chinayah from Department of Pharmacology, Faculty of Medicine, University of Malaya for their assistances in the patients recruitment and samples collection, my research assistance Mr. Megat Harris bin Mohd Aji, Miss Farah Rohaida and Miss Chan Kam Lee for helping me with data entry. My gratitude also goes to Professor Nor Zuraida Zainal, the Head of Department, Department of Psychological Medicine for allowing me to take my study leave and also for her valuable comments of my studies. I also would like to thank Mr Jagjit Singh from Mansa Pharma for his support in supplying the study medication.

Besides that, I would like to show my gratitude to Puan Roswati binti Apin, Encik Zunaide bin M Taib and all the staff at Papar Rehabilitation Centre; to Inspector Rajesh Juri and all his staff from Sabah Prison Headquarters, Kota Kinabalu, Sabah for their collaboration and permission to get the samples from drug addicts; Hospital of Luyang, Kota Kinabalu, Sabah for their kind permission to get the samples from healthy controls (pharmacogenomic study). Many thanks to the rehabilitating drug addicts and healthy volunteers who had participated in this study.

Most importantly I am truly indebted and would like to express my thanks to my beloved wife Dr. Mas Ayu Said from the Department of Social Preventive Medicine for her assistance, guidance and comments on the statistical analysis and study design, and especially for her careful editing of my dissertation. A special thanks to my adorable children Maisarah, Muhammad Akmal and Hazirah; my parents (Sulaiman Abdul Majid and Samihah Jabah) and all family members for their understanding, support, encouragement, patience and love throughout my PhD study and during my thesis preparation.

Abstract

Methamphetamine dependence remains a worldwide problem and Malaysia is no exception. The widespread of methamphetamine dependent has given an impact that can be felt at various levels, from the individual, to the individual's family, community and society.

Unfortunately, there are not many studies done on the issues of methamphetamine dependence in Malaysia. We are still lacking in published data especially in terms of prevalence, psychiatry morbidity, genetic risk factors and treatment aspect.

Based on the result of the study, we found that the prevalence of psychiatric co-morbidity was 54.4% and the prevalence of suicidality was 12.1 %. The subjects had high rates for methamphetamine-induced psychosis with 47.9% had at least one episode of psychotic symptoms and 13.0% were still having psychotic symptoms at the time of assessment.

Our results showed that the distribution of the BDNF Val66Met genotype in Chinese subjects with methamphetamine dependence and methamphetamine psychosis were significant compared with controls. The frequency of the 66Val allele in methamphetamine-dependent subjects was higher than that in the control group, suggesting that the 66Val carriers are more susceptible to methamphetamine dependence. However, 66Val allele frequency in other ethnicities was not significantly different from the controls.

Among those who were having methamphetamine-induced psychosis, treatment with aripiprazole was associated with significant decline in the Positive And Negative Symptoms Scale (PANSS) and Clinical Global Impression of Severity (CGI-S) score. Aripiprazole was generally well tolerated with no serious adverse event occur. In the randomised controlled trial study, 84.2% of participants randomized to aripiprazole completed the study compared to only 50% of the placebo group completed. There was a statistically significant difference between groups in the amount of time spent in treatment, with those given aripiprazole retained for an average of 48.7 days (\pm 4.0) compared with only 37.1 days (\pm 5.0) for the placebo group. The survival curves results showed that participants in the aripiprazole group were less likely to drop out of the study than those in the placebo group. The difference was statistically significant. Psychotic symptoms as measured by PANSS and CGI were decreased among participants who were randomized to aripiprazole treatment but those who were randomized to placebo showed an increased in the total PANSS and CGI score. However there were no statistically significant effects for aripiprazole relative to placebo on methamphetamine use verified by urine drug screen. Aripiprazole treatment was not associated with any serious adverse event.

Based on the findings:

- Support the fact that methamphetamine users are a high-risk population for psychosis.

- Suggest that the BDNF Val66Met polymorphism may contribute to methamphetamine dependence and psychosis in the Chinese population but not in other Malaysian ethnicities.
- Suggest that aripiprazole was efficacious and safe options for the treatment of methamphetamine-induced psychosis.
- Aripiprazole was no more effective than placebo in maintaining abstinence from methamphetamine use. However, it facilitated treatment retention and reduced the occurrence of psychotic symptoms in patients with methamphetamine dependence.

Abstrak

Ketagihan dadah methamphetamin masih menjadi masalah di seluruh dunia dan di Malaysia perkara tersebut tidak terkecuali. Ketagihan methamphetamin yang berleluasa ini telah mendatangkan kesan yang besar terhadap setiap individu yang terbabit, keluarga, komuniti dan setiap lapisan masyarakat.

Malangnya tidak banyak kajian yang telah dilakukan terhadap isu-isu berkaitan penagihan methamphetamin di Malaysia. Kita masih lagi kekurangan dari segi penerbitan data untuk prevalen, psikiatrik morbiditi, faktor risiko genetik dan dari segi rawatan.

Berdasarkan kajian yang dilakukan kami dapati prevalen psikiatrik ko-morbiditi adalah sebanyak 54.4% dan prevalen bunuh diri pula adalah 12.1%.

Kadar psikosis disebabkan oleh penggunaan methamphetamin adalah tinggi iaitu 47.9% daripada peserta mengalami sekurang-kurangnya satu episod simptom psikosis dan 13% dari peserta masih lagi mengalami simptom psikosis semasa kajian dilakukan.

Keputusan kami menunjukkan taburan BDNF Val66Met genotipal dikalangan peserta berbangsa Cina yang ketagih methamphetamin dan mengalami psikosis disebabkan oleh methamphetamin adalah ketara berbanding peserta kawalan. Kekerapan allele 66Val dikalangan penagih methamphetamin adalah lebih tinggi berbanding kumpulan kawalan, menunjukkan pembawa 66Val adalah lebih terdedah untuk mengalami ketagihan methamphetamin. Walau bagaimanapun

kekerapan allele 66Val untuk kumpulan etnik lain adalah tidak berbeza dengan kumpulan kawalan.

Dikalangan mereka yang mengalami psikosis disebabkan oleh methamphetamin, rawatan menggunakan aripiprazole telah menunjukkan penurunan ketara skala Positif dan Negatif Simptom(PANSS) dan skala Kesan Global Klinikal - Keterukkan (CGI-S) sepanjang tempoh kajian. Secara amnya aripiprazole tidak menimbulkan kesan sampingan yang serious.

Semasa kajian rawak terkawal, 84.2% peserta yang dirawakkan mendapat aripiprazole menamatkan kajian berbanding hanya 50% peserta yang dirawakkan mendapat placebo menamatkan kajian. Terdapat perbezaan statistik yang ketara diantara kumpulan di dalam jumlah masa kekal didalam rawatan, dengan peserta yang diberikan aripiprazole kekal didalam rawatan secara purata selama 48.7 hari (+4.0) berbanding dengan hanya 37.1 hari (+5) untuk kumpulan placebo. Keputusan lengkok kehidupan menunjukkan peserta dikumpulan aripiprazole mempunyai kebarangkalian yang kurang untuk berhenti dari kajian berbanding kumpulan yang mendapat placebo.

Simptom psikotik yang diukur menggunakan PANSS dan CGI juga menunjukkan pengurangan dikalangan peserta yang dirawakkan mendapat aripiprazole tetapi bagi peserta yang dirawakkan mendapat placebo menunjukkan peningkatan di dalam jumlah markah PANSS dan CGI. Walau bagaimanapun tidak terdapat perbezaan ketara dari segi statistik di antara kumpulan aripiprazole dan placebo untuk penggunaan methamphetamin dikalangan penagih melalui ujian dadah

air kencing. Secara amnya aripiprazole tidak menimbulkan kesan sampingan yang serious.

Berdasarkan kepada keputusan kajian:

- Menyokong fakta bahawa penagih methamphetamin adalah terdedah kepada risiko untuk mendapat psikosis .
- Mencadangkan bahawa polimorfisme BDNF Val66Met mungkin menyumbang kepada ketagihan methamphetamin dan psikosis di kalangan etnik Cina tetapi tidak kepada etnik-etnik lain di Malaysia.
- Aripiprazole mengurangkan simptom psikotik disebabkan oleh penagihan methamphetamin dan rawatan tersebut tidak menimbulkan kesan sampingan yang serious.
- Aripiprazole tidak lebih berkesan berbanding placebo untuk mempertahankan pantang dari penggunaan methamphetamin. Bagaimanapun aripiprazole membantu peserta terus kekal dalam rawatan dan dapat mengurangkan kejadian psikotik dikalangan penagih methamphetamin.

Contents

Original Literary Work Declaration	i
Acknowledgements	v
Abstract.....	vii
Contents	xiii
Tables.....	xvii
Publications	xxi
Abbreviations.....	xxv
Chapter ONE: INTRODUCTION.....	1
1.1 Background and Conceptual Framework.....	1
1.2 What is Amphetamine-Type Stimulant (ATS)?	7
1.3 Types of methamphetamine and routes of administration	7
1.4 ATS production.....	10
1.5 Mechanism of Action of methamphetamine and Ecstasy.....	12
1.6 ATS abuse and dependence	14
1.7 Primary form of ATS abused in Asia and Pacific.....	15
1.8 Illicit drug market in Malaysia.....	16
1.9 Legal framework towards illicit drug abuse and trafficking.....	17
1.10 Drug-related offence arrestment and seizures in Malaysia 2009	19
1.11 Demographic of drug users in Malaysia 2009	21
1.12 Problems associated with ATS or general drug abuse.....	27
1.13 Medical complications of ATS abuse	30
1.14 Effects on other areas of health.....	34
Chapter TWO: Psychiatric Co-morbidity and Suicidality in Methamphetamine Dependence	39
2.1 Abstract	39
2.2 Introduction.....	41
2.3 Methodology	46

2.4 Results.....	53
2.5 Discussion.....	59
2.6 Conclusions.....	67
Chapter THREE: Prevalence and Association of Methamphetamine-Induced Psychosis	69
3.1 Abstract.....	69
3.2 Introduction.....	72
3.3 Methodology.....	75
3.4 Results.....	82
3.5 Discussion.....	90
3.6 Conclusions.....	97
Chapter FOUR: Association of Brain-Derived Neurotrophic Factor (Val66Met) Genetic Polymorphism with Male Methamphetamine Dependence in Malaysia.....	99
4.1 Abstract.....	99
4.2 Introduction.....	102
4.3 Methodology.....	109
4.4 Results.....	117
4.5 Discussion.....	127
4.6 Conclusions.....	131
Chapter FIVE: Efficacy and Safety of Aripiprazole in the Treatment of Methamphetamine-Induced Psychosis: An Open Label Prospective Study	132
5.1 Abstract.....	132
5.2 Introduction.....	135
5.3 Systematic review on the efficacy and safety of aripiprazole in the treatment of methamphetamine-induced psychosis	146
5.4 Methodology.....	155
5.5 Results.....	182
5.6 Discussion.....	194
5.7 Conclusions.....	200

Chapter SIX: Randomized Placebo-Controlled Trial of the Safety and Efficacy of Aripiprazole in the Treatment of Methamphetamine Dependence Patients.....	201
6.1 Abstract	201
6.2 Introduction.....	204
6.3 Systematic review on the aripiprazole as treatment of amphetamine and methamphetamine dependence patients	215
6.4 Methodology	224
6.5 Results.....	250
6.5 Discussion	265
6.6 Conclusions.....	275
Chapter SEVEN: Overall Conclusions and Recommendations...	276
7.1 Overall Conclusions.....	276
7.2 Recommendations	284
Appendix A - Operational Definitions	287
Appendix B - Mini International Neuropsychiatric Interview (M.I.N.I.)	289
Appendix C - Amphetamine Withdrawal Questionnaire (AWQ)	316
Appendix D - Brief Substance Craving Scale (BSCS)	317
Appendix E - Abnormal Involuntary Movement Scale (AIMS) ..	318
Appendix F- Barnes Akathasia Scale (BARS).....	320
Appendix G - Simpson Angus Scale (SAS).....	322
Appendix H - Hospital Anxiety and Depression Scale (HADS) .	326
Appendix I - Positive and Negative Symptoms Scale(PANSS) ..	328
Appendix J - Clinical Global Impressions Scale (CGI-S)	330
Appendix K- Approval Letter from Ethical Committee/ Government Authorities	331
Appendix L - Research Grant.....	338

Appendix M - Advertisement in Newspapers	340
Appendix N - Article write up in Newspaper : Berita Harian and China Press	341
Appendix O - Oral and Poster Presentation	343
Appendix P - Publications	354
References	366

Tables

<u>Table</u>	<u>Title</u>	<u>Page</u>
Table 1.1:	Comparison of the total arrestment of drug offenders under the Dangerous Drug Act 1952 between 2008 and 2009	19
Table 1.2:	Comparison of ATS seized between 2008 and 2009	20
Table 1.3:	Comparison of property seized under Property Forfeiture Act 1988 between 2008 and 2009.....	20
Table 1.4:	Comparison of drug users identified between 2008 and 2009	21
Table 1.5:	Comparison of drug users identified by ethnic between 2008 and 2009.....	22
Table 1.6:	Comparison of drug users identified by types of drug between 2008 and 2009	25
Table 1.7:	Comparison of ATS users identified by ethnic and types of drug abuse.....	26
Table 1.8:	Signs indicating a person might be using methamphetamine.....	31
Table 1.9:	Major signs and symptoms of ATS toxicity	38
Table 2.1:	Association between Demographic Characteristics and Suicidality among Methamphetamine Dependence	55
Table 2.2:	Association between Axis I Psychiatric Disorders and Suicidality among Methamphetamine Dependence	56
Table 2.3:	Association between Drug Use History and Suicidality among Methamphetamine Dependence	57
Table 2.4:	Independent Predictors for Suicidality among Methamphetamine Dependence Patient.....	58
Table 3.1:	Association between Demographic Characteristics and Psychosis among Methamphetamine Dependence Patients	85
Table 3.2:	Clinical Symptom Profiles of Patients with Methamphetamine Psychosis (Elicited By the Use of MINI).....	86
Table 3.3:	Association between Axis I Psychiatric Disorders and Psychosis among Methamphetamine Dependence Patients	87
Table 3.4:	Association between Drug Use History and Psychosis among Methamphetamine Dependence Patients	88
Table 3.5:	Independent Predictors for Psychosis Among Methamphetamine Dependence Patients	89

Table 4.1:	Demographic data for the male methamphetamine-dependent and the male control subjects	120
Table 4.2:	Genotype frequencies of the <i>BDNF</i> Val66Met polymorphism in male controls and male methamphetamine-dependent subjects.	121
Table 4.3:	Allelic frequencies of the <i>BDNF</i> Val66Met polymorphism in male controls and male methamphetamine-dependent subjects	122
Table 4.4:	The odds ratio with comparison between allele and genotype frequencies of the <i>BDNF</i> Val66Met polymorphism in Chinese controls and Chinese methamphetamine-dependent subjects.....	123
Table 4.5:	The odds ratio with comparison between allele and genotype frequencies of the <i>BDNF</i> Val66Met polymorphism in controls and methamphetamine-dependent subjects.	123
Table 4.6:	Genotype frequencies of the <i>BDNF</i> Val66Met polymorphism in male methamphetamine-dependent subjects with and without psychosis.	124
Table 4.7:	Allelic frequencies of the <i>BDNF</i> Val66Met polymorphism in male methamphetamine-dependent subjects with and without psychosis.	125
Table 4.8:	The odds ratio with comparison between allele and genotype frequencies of the <i>BDNF</i> Val66Met polymorphism in methamphetamine-dependent subjects with psychosis and methamphetamine-dependent subjects without psychosis.....	126
Table 4.9:	The odds ratio with comparison between allele and genotype frequencies of the <i>BDNF</i> Val66Met polymorphism in Chinese methamphetamine-dependent subjects with psychosis and methamphetamine-dependent subjects without psychosis.....	126
Table 5.1:	Treatment of acute methamphetamine-induced psychosis	137
Table 5.2:	Study visit plan for the treatment of aripiprazole among methamphetamine-induced psychosis patients	174
Table 5.3:	Socidemographic and drug history of methamphetamine- induced psychosis subjects	185
Table 5.4:	Baseline characteristics of efficacy and safety measures	186
Table 5.5:	Primary and secondary efficacy variables – Changes from baseline at Day 4*	189
Table 5.6:	Primary and secondary efficacy variables – Changes from baseline at Day 7*	190
Table 5.7:	Primary and secondary efficacy variables – Changes from baseline at Day 14*	191

Table 5.8: Mixed-model repeated measures (MMRM) analyses of primary and secondary efficacy at baseline, day 4, day 7 and day 14.....	191
Table 5.9: Number (%) of Patients reporting Adverse Events – Safety Population	192
Table 5.10: Primary Safety variables – Changes from baseline at Day 4, 7 and 14	193
Table 6.1 Systematic review on the aripiprazole as treatment of methamphetamine dependence patients.....	218
Table 6.2 Systematic review on the aripiprazole as treatment of amphetamine dependence patients.....	219
Table 6.3 Sociodemographic characteristics of methamphetamine dependence subjects	256
Table 6.4 Drug history of methamphetamine dependence subjects	257
Table 6.5 Proportion of methamphetamine-positive urine screens for aripiprazole and placebo	258
Table 6.6 Generalized Estimating Equations(GEE) analysis for methamphetamine urine screens between aripiprazole and placebo	259
Table 6.7 Number (%) of patients reporting adverse events – safety population.....	261
Table 6.8 Concomitant medications and the indication according to treatment group	261
Table 6.9 BARS safety measures - changes from baseline at day 14, and day 42.....	262
Table 6.10 SAS and AIMS safety measures - changes from baseline at day 14, and day 42	262
Table 6.11 Aripiprazole dosage among the methamphetamine dependence patients	262
Table 6.12 PANSS and CGI efficacy measure for psychotic symptoms....	263
Table 6.13 Mixed Model Repeated Measures (MMRM) for PANSS and CGI among methamphetamine dependence patients	263
Table 6.14 Brief Substance Craving Scale (BSCS) efficacy measures, HADS efficacy measures for anxiety and depressive symptoms.	264
Table 6.15 Mixed Model Repeated Measures (MMRM) for HADS-Anxiety, HADS-Depression and BSCS among methamphetamine dependence patients	264

Figures

<u>Figure</u>	<u>Title</u>	<u>Page</u>
Figure 1.1	Conceptual Framework	6
Figure 1.2	Production of amphetamine and methamphetamine	11
Figure 1.3	Production of MDMA	12
Figure 4.1	Gel photo of 2.5% (w/v) agarose gel electrophoresis for detection of BDNF Val66Met polymorphism	120
Figure 5.1	Flow chart showing the article-identification process for methamphetamine-induced psychosis.....	149
Figure 5.2	Flow chart showing the article-identification process for amphetamine-induced psychosis.....	149
Figure 6.1	Flow chart showing the article-identification process for methamphetamine dependent.....	217
Figure 6.2	Flow chart showing the article-identification process for amphetamine dependent.....	217
Figure 6.3	The overall study design for methamphetamine-induced psychosis and methamphetamine dependence study	224
Figure 6.4	Disposition of patients in the randomized controlled trial between aripiprazole and placebo for methamphetamine dependence patients	255
Figure 6.5	Methamphetamine positive urine screens by visit	258
Figure 6.6	Kaplan-Meier estimate of the survivor function for retention in treatment.....	260

Publications

The following papers have been published or submitted from this thesis:

Journals

1. A Hatim. Amphetamine Type Stimulant (ATS) Induced Psychosis: A Rising Problems in Malaysia. Malaysian Journal of Psychiatry Dec 2008, 17(2): 3-6
2. A Hatim, M Ayu, H Habil, M Mustafa. Safety and efficacy of aripiprazole in the treatment of amphetamine and methamphetamine induced psychosis: a preliminary result. World Journal of Biological Psychiatry, 2009,10(1):403
3. A Hatim, M Ayu, H Habil .Prevalence of drug induce psychosis among amphetamine and methamphetamine dependence patients. World Journal of Biological Psychiatry, 2009;10(1):403
4. A Hatim, M Ayu, H Habil. Psychiatric co-morbidity among patients with amphetamine and methamphetamine dependence in Malaysia. European Neuropsychopharmacology, 2009;19(3): S654-S655
5. M S Sim, Z Mohamed, A Hatim, V L Rajagopal, M H Habil. Association of brain-derived neurotrophic factor (Val66Met) genetic polymorphism with methamphetamine dependence in a Malaysian population. Brain Research August 2010, 1357:91-9
6. A. Hatim, S. Mas Ayu, H. Habil, M. Mustafa, J. Gill, R. Rusdi and A. Amer Siddiq. Psychiatric co-morbidity and suicidality among methamphetamine dependent patients who seek treatment in Malaysia. European Neuropsychopharmacology, 2011,21(2): S161

7. A.H. Sulaiman, J.S. Gill, M.A Said, N.Z. Zainal, M.H. Habil, N.C. Guan. A randomized, placebo controlled trial of aripiprazole for the treatment of methamphetamine dependence and associated psychosis. International Journal of Psychiatry in Clinical Practice. 2012 (in press).
8. A.H. Sulaiman, J.S. Gill, M.A Said, N.Z. Zainal, M.H. Habil, N.C. Guan. An open label study of aripiprazole for methamphetamine induced psychosis. Bulletin of Clinical Psychopharmacology. 2012 (under review).

Presentation in Conference

1. Safety and efficacy of aripiprazole in the treatment of amphetamine and methamphetamine induced psychosis: a preliminary result. Presented at 9th World Biological Psychiatric Conference, July 2009, Paris, France.
2. Prevalence of drug induce psychosis among amphetamine and methamphetamine dependence patients. Presented at 9th World Biological Psychiatric Conference, July 2009, Paris, France.
3. Prevalence of psychiatric co-morbidity among amphetamine and methamphetamine dependence patients. Presented at the European Collegium Neuropsychopharmacology (ECNP) 11-16 September 2009 Istanbul, Turkey.
4. The scourge about designer drugs. Presented at the 6th National Conference on Addiction Medicine 23-25 October 2009 Kuala Lumpur, Malaysia.
5. Substance abuse perils issues and solutions. Presented at the Seminar by Malaysia Medical Association on 25 April 2010 Kuala Lumpur, Malaysia.
6. Methamphetamine psychosis. Presented at the 12th Johor Mental Health Convention 1 - 4 June 2010 Johor Bahru, Malaysia.
7. Methamphetamine dependence in Malaysia. Presented at the 7th Kuala Lumpur Mental Heath Conference 2010 26-28 July 2010 Kuala Lumpur, Malaysia.

8. Prevalence of psychiatric co-morbidity and suicidality among methamphetamine dependence patients. Presented at the European Collegium Neuropsychopharmacology (ECNP) 14-16 April 2011 St. Petersburg, Russia.

Abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
AIMS	Abnormal Involuntary Movement Scale
APAIC	Asia and Pacific Amphetamine-type Stimulants Information Centre
ATS	Amphetamine-Type-Stimulants
AWQ	Amphetamine Withdrawal Questionnaire
BARS	Barnes Akathasia Scale
BDNF	Brain-Derived Neurotrophic Factor
BSCS	Brief Substance Craving Scale
CGI-S	Clinical Global Impression Scale - Severity of Illness
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
DAT	Dopamine Transporter Gene
DBH	Dopamine Beta-Hydroxylase Gene
DRD	Dopamine Receptor Genes
EC	Ethic Committee
FAAH	Fatty Acid Amide Hydrolase Gene
GDP	Gross Domestic Product
GEE	Generalized Estimating Equation
HADS	Hospital Anxiety Depression Scale
INCSR	International Narcotics Control Strategy Report
ITT	Intention to Treat
KDRM	Royal Malaysian Custom
KLIA	Kuala Lumpur International Airport

LOCF	Last Observation Carried Forward
M.I.N.I.	Mini International Neuropsychiatric Interview
MATES	Methamphetamine Treatment Evaluation Study
MDMA	3,4-methylenedioxymethamphetamine
Met	Methionine
MMRM	Mixed-effects model repeated-measures
NADI	Malaysian National Drug Information System
PANSS	Positive and Negative Syndrome Scale
PAWE	Power of Association With Errors
PDRM	Royal Malaysian Police
PI	Principle investigator
RFLP	Restriction Fragment Length Polymorphism
SAE	Serious Adverse Event
SAS	Simpson Angus Scale
SOD2	Superoxide Dismutase 2
SPSS	Statistical Package for Social Sciences
TRAR4	Trace Amine Receptor Gene 4
UMMC	University Malaya Medical Centre
UNODC	United Nations Office on Drugs and Crime
Val	Valine

1 Introduction

Chapter ONE: INTRODUCTION

1.1 Background and Conceptual Framework

Substance dependence remains a worldwide problem and Malaysia is no exception. Substance dependence, characterized by compulsive uncontrollable drug use despite clear negative consequences, is among the most prevalent psychiatric disorders, contributing significantly to mortality, physical and social morbidity.

The United Nations Office on Drugs and Crime (UNODC) estimated that in 2007, 26 million people in the world have used methamphetamine, 21 million have used opiates and 20.7 million have used cocaine (Unodc, 2009a). The past decade has seen a remarkable increase in the popularity of methamphetamine within East Asia and the Pacific region. It was also reported that 60% of methamphetamine users live in Asia, and that misuse of this illicit substance has become a major problem in countries such as China, Philippine, Myanmar, Thailand and Malaysia (Unodc, 2009a).

In Malaysia, within the first three months of 2010, the National Anti-Drug Agency has identified 3,611 who are substance dependent, which is an increase of about 110% compared to the same period in the previous year. Among these identified addicts, 18% were dependent on amphetamine-type-stimulants (ATS), which include amphetamine, methamphetamine and ecstasy pills. This represents a 117% increase in ATS addicts compared with the same period in the previous year (Kdn, 2010).

1 Introduction

The Malaysian government has declared that drug addiction is the number one enemy of the country (Afp, 2000). One of the initiatives against drug abuse and trafficking taken by Malaysian government is the launching of the 'drug-free by 2015' policy (Utusan, 2006). This long-term effort aims to reduce domestic drug use to negligible levels by 2015. The Malaysian government spent more than RM 1.5 billion over the past five years trying to make this policy a reality (Nst, 2010). In order to show its seriousness in combating drug problem, Malaysia strictly enforces its drug laws. Possession, use, and trafficking in illicit drugs in Malaysia are severe criminal offences. Malaysian legislation provides for a mandatory death penalty for convicted drug traffickers (Akta, 1952).

The widespread of methamphetamine dependence has given an impact that can be felt at various levels, from the individual, to the individual's family, community and society. At the country level, methamphetamine dependence gives rise to serious behavioural, medical and psychiatric consequences, imposing an immense burden on the medical, public health and criminal justice systems.

According to a 2004 research on the socio-economic impact of ATS (Wilkins *et al.*, 2004), it was reported that about one third of those who had used an ATS drug in the last year reported experiencing harm in at least one area of their lives from the use of these drug. About half of the frequent methamphetamine users reported harm in the areas of friendship and social life (55%), health (55%), and energy and vitality

1 Introduction

(53%). Work and work opportunities were also rated as seriously affected by frequent methamphetamine users.

More recently, methamphetamine use has also been associated with increased crime and violence such as feuds between trafficking gangs, robbery, homicide (Kosten and Singha, 1999). Compared with other psychoactive drugs, chronic methamphetamine use is more closely related to violent behaviour.

On a wider scope, illicit drug use and trafficking also poses a significant impact on the economic sectors in consumer countries. Important and valuable resources are sacrificed, diverting from legitimate and more sustainable investments to drug production and consumption, which in turn impacts negatively on the productivity of the users (Unodc, 1998b). Drug abuse also raises the government expenditure, the largest part of which is used for drug-related crime and law enforcement costs (Unodc, 1998b). For instance, the Malaysian government has to spend more than RM300 million each year in its endeavour against illicit drug activities, half of which are used to set up rehabilitation centres (Utusan, 2006).

On the individual level, the increasing trend in methamphetamine use raises particular concern because of its deleterious effects on individuals and related health costs. The health costs of a drug addict have been reported to be almost 80% higher than those of an average citizen (Unodc, 1998b). Methamphetamine consumption is constantly linked to high-risk HIV behaviours (Semple *et al.*, 2004, Kurtz and

1 Introduction

Inciardi, 2003, Reback *et al.*, 2004, Marshall *et al.*, 2011) and more recently, cardiovascular problems (Mau *et al.*, 2009, Kaye *et al.*, 2007, Droogmans *et al.*, 2007, De Silva *et al.*, 2007). The most serious problem, however, reported by frequent methamphetamine users was psychological rather than physical. About two-thirds of frequent methamphetamine users reported anxiety, mood swings, short temper, paranoia and depression, while 21% of them reported suicidal thoughts and 13% suicide attempts after using the drug (Wilkins *et al.*, 2004). As a potent psycho-stimulant with a high dependence liability, methamphetamine dependence is closely associated with the risk of acute and chronic psychological disturbance, including psychosis (Who, 1997).

Unfortunately, there are not many studies done on the issues of methamphetamine dependence in Malaysia. We are still lacking in published data especially in terms of prevalence, psychiatry morbidity, genetic risk factors and treatment aspect.

My study will focus on few important issues related to methamphetamine dependence including:

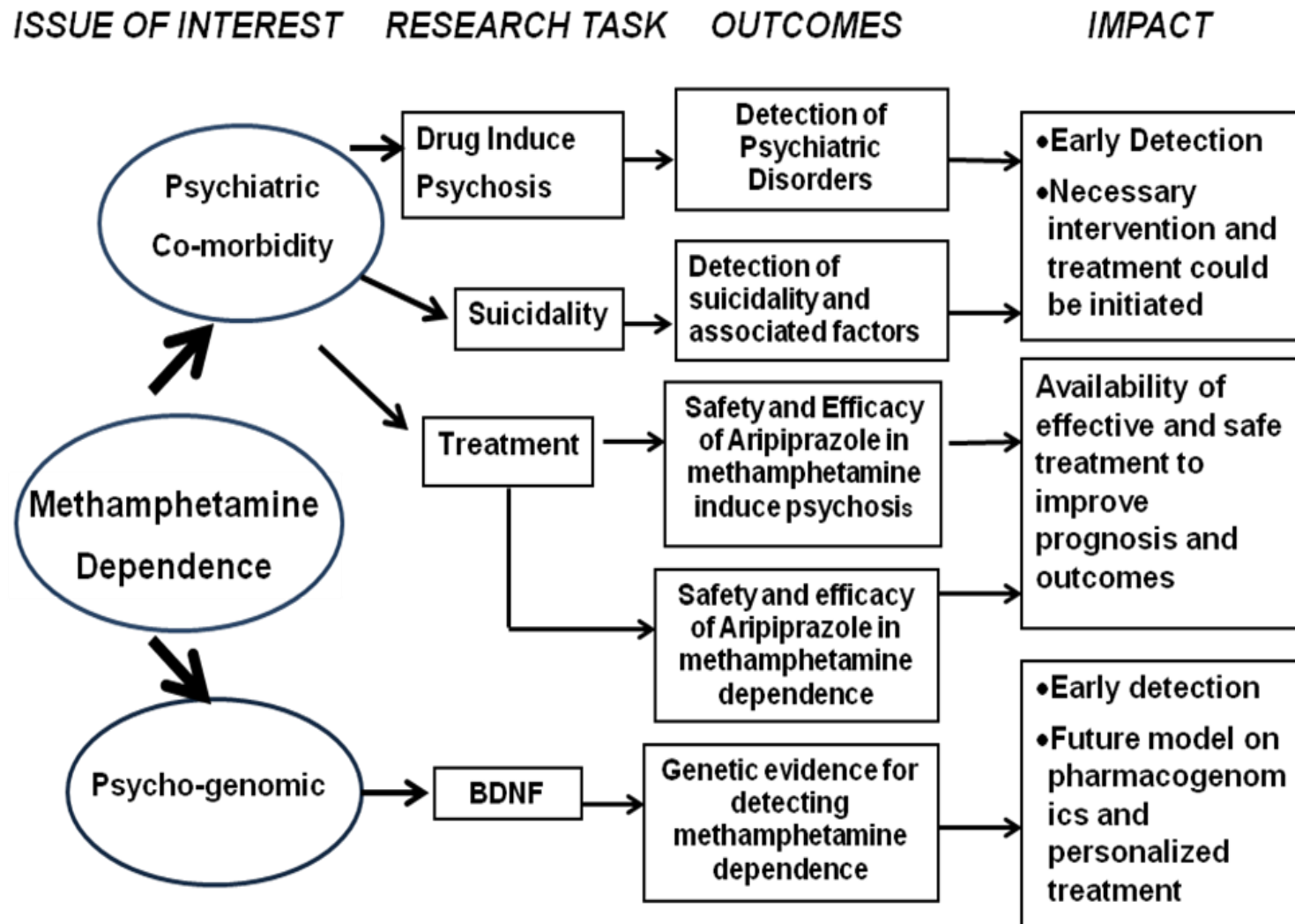
1. Psychiatric comorbidity and suicidality among treatment seeking methamphetamine dependence patients.
2. Prevalence and associations of methamphetamine psychosis among treatment seeking methamphetamine dependence patients.

1 Introduction

3. Association of brain-derived neurotrophic factor (Val66Met) genetic polymorphism with male methamphetamine dependence in Malaysia.
4. Open label study of the safety and efficacy of aripiprazole in the treatment of methamphetamine induced psychosis.
5. Randomized placebo controlled trial of the safety and efficacy of aripiprazole in the treatment of methamphetamine dependence.

1 Introduction

Figure 1.1 Conceptual Framework



1 Introduction

1.2 What is Amphetamine-Type Stimulant (ATS)?

Amphetamine-type stimulants (ATS) in general refer to a group of psychothropic drugs whose principal members include **amphetamine**, **methamphetamine** (pharmaceutically known as methylamphetamine), and **3,4-methylenedioxymethamphetamine (MDMA or 'Ecstasy')**. Other substances that also fall into this category of drug are such as methcathinone, fenetylline, ephedrine, pseudoephedrine, methylphenidate (Who, 2011).

ATS are sometimes prescribed for medical reasons, mainly in the treatment of attention-deficit hyperactivity disorder (ADHD) in adults and children (Bejerot *et al.*, 2010, Swanson *et al.*, 2010), as well as symptoms of traumatic brain injury (Warden *et al.*, 2006) and drowsiness in narcolepsy (Bruck *et al.*, 2005) and chronic fatigue syndrome (Blockmans *et al.*, 2006). Unfortunately, today these drugs, mainly amphetamine, methamphetamine and MDMA, are illegally used for recreational purposes in clubs and discos, leading to various consequences.

1.3 Types of methamphetamine and routes of administration

ATS come in different forms and with different names. The route of administration for each form also varies. While smoking, sniffing, inhaling and injecting are the most popular methods of ATS use, but ways of using the drug differ widely across the region (Unodc, 2009e).

The primary forms of ATS in East Asia and the Pacific include crystals ('ice'), methamphetamine powder, tablets/pills, MDMA/Ecstasy, and

1 Introduction

"base" (Unodc, 2009e). Methamphetamine found on the street comes in the form of powder, crystals or pills. It is white, odourless, bitter-tasting, and easily dissolves in water or alcohol. The substance is often adulterated with chemicals that were used to synthesize it.

i). **Crystal methamphetamine**

'Ice', also known as 'Crystal', 'glass' or 'syabu', is purified form of methamphetamine that has been 'washed' in a solvent to remove impurities. The purity level of this form of methamphetamine is usually above 80% (Unodc, 2009e, Doj, 2010), and thus has longer-lasting physical effects. It can be smoked in a glass pipe or on a piece of aluminium foil (known as 'chasing the dragon'). 'Ice' is also sometimes administered via snorting, swallowing or injection.

ii). **Methamphetamine powder**

'Speed' ('meth', 'crank') is a powdered methamphetamine of relatively low purity and sold in grams or ounces. Its colour ranges from dingy white to reddish brown. It can be snorted or injected. It can also be orally ingested or smoked. It is not common in Southeast Asia, but has been found in Cambodia, Indonesia, Japan and Thailand. However, it is the most popular form of methamphetamine in Australia and the US (Unodc, 2009e, Unodc, 2009c).

iii). **Methamphetamine tablets/pills**

Methamphetamine tablets/pills, which are generally a composite of methamphetamine and caffeine, are often referred to by their Thai

1 Introduction

name, yaba ("crazy medicine").(Unodc, 2009e) Tablets are the predominant form of methamphetamine used in mainland Southeast Asia - Cambodia, Lao PDR, Thailand, and Vietnam. Pills are often ingested orally, and they can also be crushed into powder for inhalation, or dissolved in water for injection (Unodc, 2009c).

iv). **MDMA/Ecstasy**

A hallucinogen marketed as a 'feel good drug', MDMA is mainly used as a recreational drug. MDMA is a chemical derivative of methamphetamine, but is less common than methamphetamine in Southeast Asia.

MDMA comes in the form of powder or crystal, and is used by snorting, or by oral administration either by applying a dab to the tongue and washing it down with water, or mixing it into a drink. The white MDMA is also mixed with substances, such as chalk, to form tablets (e.g. Ecstasy) or pills, or filled in capsules. In many parts of the world, however, the usage of plain MDMA powder instead of pills is popular.

Ecstasy is usually sold as tablets of various shapes and colours, and imprinted with monograms. It can also be found in the form of capsules. The predominant form of ingestion is swallowing (Unodc, 2009c).

v). **Base methamphetamine**

A damp, sticky powder that has a yellow or brown hue due to the presence of impurities. 'Base' is manufactured and more commonly

1 Introduction

used in Australia than in countries in the Southeast Asia (Jenkinson and Johnston, 2006). This type of methamphetamine generally requires heating to sufficiently dissolve it for injection (Unodc, 2009e).

1.4 ATS production

ATS are synthetic central nervous system (CNS) stimulants manufactured in laboratories. The manufacturing process requires various types of substances, precursors, chemical reagents and solvents, mixing and heating equipment to synthesize ATS. Other equipment is required to make ATS tablets.

i). Producing amphetamine and methamphetamine

Methamphetamine can be quite easily produced in clandestine laboratory, as the required ingredients are commercially available and relatively inexpensive. In addition, the manufacture process does not need specialised equipment or advanced technical skills. Perhaps these are part of the reasons why methamphetamine is a drug with high potential of widespread abuse.

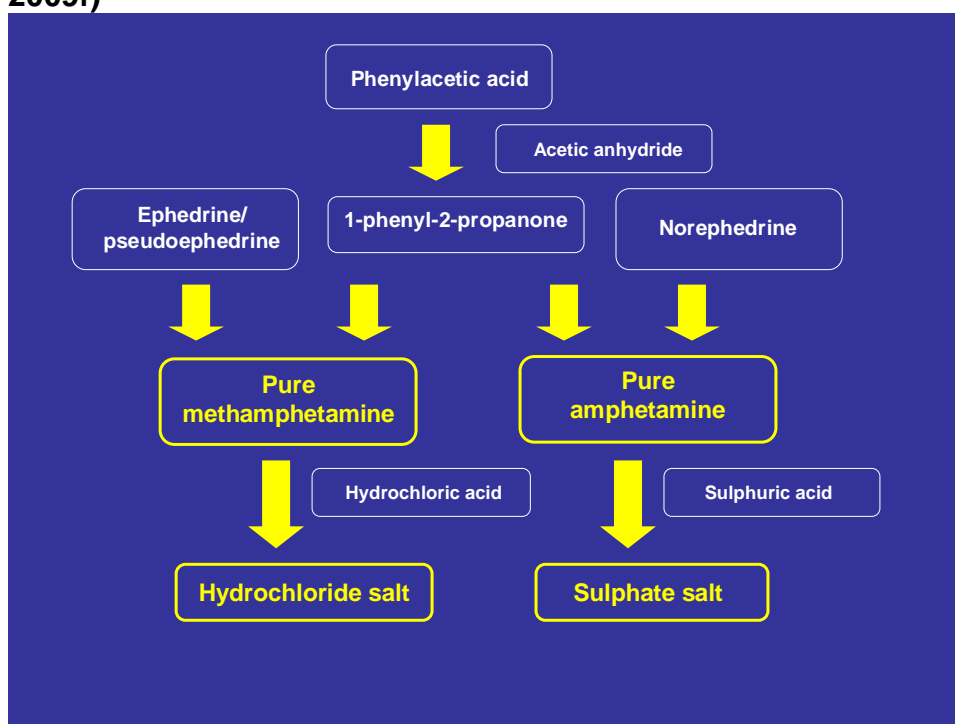
While norephedrine is the precursor that is converted to amphetamine, ephedrine is the precursor for methamphetamine. A reduction process is carried out by adding a reducing reagent, such as acetic anhydride, to produce pure amphetamine or methamphetamine (Figure 1.2) (Unodc, 2009f).

Pure methamphetamine and amphetamine have the chemical characteristics of bases, which are both lipid-soluble and volatile, and

1 Introduction

thus chemically and physically less stable. Therefore these amphetamines must be mixed with acids to produce a salt. For example, hydrochloric acid or sulphate acid is added to the amphetamine base to produce amphetamine hydrochloride powder that is water-soluble and chemically more stable. Therefore most amphetamines are marketed in their crystalline form.

Figure 1.2 Production of amphetamine and methamphetamine (Unodc, 2009f)

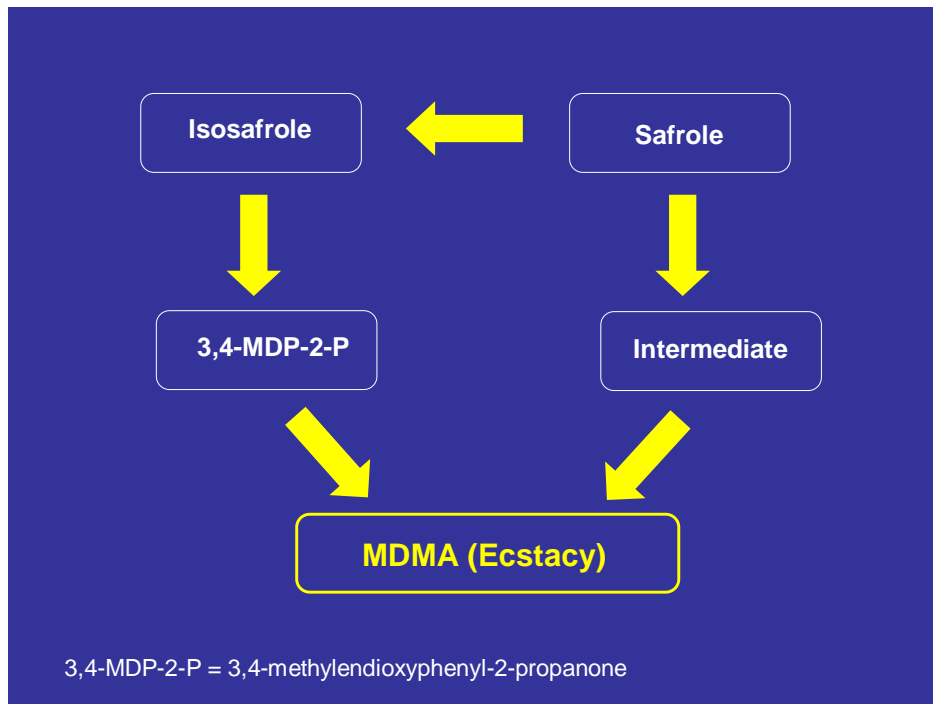


ii). Producing MDMA

The precursors and intermediate products in the manufacturing process of MDMA are outlined below (Figure 1.3) (Unodc, 2009f). The term 'ecstasy' specifies the tablet form of MDMA, although it is occasionally found in crystalline form or liquid form.

1 Introduction

Figure 1.3 Production of MDMA(Unodc, 2009f)



iii). Producing 'ice'

To make the 'ice', methamphetamine hydrochloride is added slowly to water and then brought to a temperature of just under 100°C, thus forming a super-saturated solution.(Derlet and Heischouer, 1990) The solution is then allowed to cool and the 'ice' precipitates from the solution itself to become large crystals. The ephedrine required in the production can be extracted from over-the-counter cold and flu medicines, although it can also be obtained from the black market (Mcketin *et al.*, 2005).

1.5 Mechanism of Action of methamphetamine and Ecstasy

Although both methamphetamine and Ecstasy are CNS stimulants, they produce different chemical interactions in the brain.

1 Introduction

i). **Methamphetamine**

Abusers of methamphetamine often follow the “binge and crash” abuse pattern (Gard, 2004). Once enters the body, methamphetamine works directly on the brain, causing a release of high levels of dopamine – the neurotransmitter that stimulates the brain cells and regulate feelings of pleasure. This artificially raises the dopamine level and a person feels extra good or “high”, followed by increased mental alertness, decreased appetite and a general sense of well-being (Gard, 2004).

The pleasurable effects of methamphetamine dissipate before the drug levels drop. Therefore users usually binge on methamphetamine by taking it continuously for several days. The drug does not produce energy, but permits access to energy reserves in the body. Once the effects of methamphetamine wear off, i.e. the energy reserves are used up, the body must replenish them. This leads to the “crash”, and the exhausted abuser experiences withdrawal symptoms such as depression, paranoia and aggression (Gard, 2004). To get rid of these undesirable feelings, the person takes more methamphetamine, resuming the binge-and-crash cycle all over again.

As doses administered increase, tolerance develops. Consequently, drug abusers need to take even higher doses to reach the same effect. Therefore when used long term, methamphetamine causes very strong dependence.

ii). **MDMA**

MDMA primarily affects the serotonin (Unodc, 2009e), a neurotransmitter that plays an important role in regulating mood and emotions, sexual activity, sleep, and sensitivity to pain.

Compared with methamphetamine, MDMA causes greater serotonin release and lesser dopamine release. The excess release of serotonin by MDMA likely causes a mood elevation in MDMA users, producing an energizing effect, as well as distortions in time and perception and enhanced enjoyment from tactile experiences (Unodc, 2009d).

However, by releasing large amounts of serotonin, the brain becomes markedly depleted of this important neurotransmitter, thus contributing to negative behavioural after-effects that last several days after taking MDMA.

1.6 ATS abuse and dependence

From the United Nation Office on Drugs Crimes(UNODC), an estimate of 50 million people in the world used ATSs compared with 21 million who used opiates and 20.7 million who used cocaine in 2007 (Unodc, 2009a). It was also reported that 60% of ATS users (mostly methamphetamine users) live in Asia.

Amphetamines, particularly methamphetamines, are among the most commonly abused illicit stimulants in the United States (US). According to their 2001 National Household Survey on Drug Abuse (Dhhs, 2001),

1 Introduction

the number of new methamphetamine users more than doubled between 1990 and 2000, an increase from 164,000 to 344,000 over 10 years. Among the new users, half of them aged between 12 and 17 years. The rising number of ATS abuse is also reflected in the increased number of treatment admissions of persons with primary methamphetamine use problems, from 21,000 in 1993 to 117,000 in 2003 (Baskin-Sommers and Sommers.I, 2006).

There is evidence that some individuals used ATSs in the work arena. As shown in the Quest Diagnostics' 2003 Drug Testing Index, there was an increased use of amphetamines among general US workforce employees, from 0.34% in 2002 to 0.49% in 2003, which is a whopping 44% increase (Quest-Diagnostics, 2003).

1.7 Primary form of ATS abused in Asia and Pacific

According to a 2006 report from the Asia and Pacific Amphetamine-type Stimulants Information Centre (APAIC) (Unodc, 2009c), methamphetamine in pill form ('yama'/'yaba') is the primary ATS drug of abuse in China, Cambodia, Lao PDR, Thailand and Vietnam. On the other hand, crystal methamphetamine ('ice', street name for 'syabu') is the main form of ATS abused in Malaysia, Brunei, Japan, the Philippines and Singapore. In Australia and Indonesia, the principal ATS drug of abuse is Ecstasy.

While some countries showed a stable or increaseasing trend in the use of ATS, Malaysia reported a decreased abuse trend of crystalline

1 Introduction

methamphetamine and Ecstasy from the year 2004 to 2006 (Unodc, 2009c).

Despite the seemingly declining trend of ATS abuse in Malaysia, the International Narcotics Control Strategy Report (INCSR) 2007(Bureau, 2007) actually suggested that domestic abuse in Malaysia itself is increasing and that methamphetamine production from clandestine laboratories in Malaysia are getting bigger.

This can be observed from the fact that, among others, one 'superlab' was seized in 2004 and another in 2006 in Kulim (Unodc, 2009c). In April 2007, the Narcotics Crime Investigations Department busted one large syabu producing laboratory in Johor, followed by another one in Klang, of which was believed to be the largest-ever syabu processing laboratory seized so far in Malaysia (Star, 2007).

In the Asia and Pacific region, 64 clandestine drug laboratories producing methamphetamine were seized in 2006, a number that was a third higher compared with 2005 and almost four times of that seized in 2004 (Unodc, 2009c). In addition, more than 75% of the methamphetamine laboratory seizures during 2005 and 2006 occurred in China (Unodc, 2009c).

1.8 Illicit drug market in Malaysia

Although Malaysia is not a major source country of illicit drug market, Malaysian labs are increasing methamphetamine production and the country's drug addiction rates are on the rise.

1 Introduction

Drugs are also smuggled across Malaysian borders from different parts of the world (Unodc, 2009b). Heroin and marijuana are imported from the production areas of Golden Triangle area, while ketamine comes from India. These drugs are either consumed domestically or transit Malaysia to other several countries in the region. For example, Ecstasy from Amsterdam is flown into Kuala Lumpur International Airport (KLIA) for domestic use and distribution to Thailand, Singapore, and Australia.

1.9 Legal framework towards illicit drug abuse and trafficking

i). International framework

Internationally there are several agreements and legal frameworks established towards illicit drug abuse and trafficking, including:(Unodc, 2011)

- United Nations Drug Control Conventions (1961, 1971, 1988)
- Global Assessment Programme (1998)
- ASEAN Plan of Action on Drug Abuse Control (1996)
- ASEAN and China Cooperative Operations in Response to Dangerous Drugs (ACCORD) Plan of Action (2000)
- Memorandum of Understanding (MOU) on Drug Control (1993)
- Subregional Action Plan (2000)
- Tokyo Conference on ATS (2000)
- 28th Meeting of Heads of National Drug Law Enforcement Agencies, Asia and the Pacific, in Bangkok (2004)

1 Introduction

- Regional Government Responses

Malaysia is a party to the 1988 United Nations Drug Control Convention, as well as a member of the ASEAN and ACCORD Plan of Actions.

ii). **Malaysia's initiative and law enforcement against drug-related offence**

One of the initiatives against drug abuse and trafficking of the Malaysian government is the launching of the 'drug-free by 2015' policy in 2003 (Nst, 2010). This long-term effort aims to reduce domestic drug use to negligible levels by 2015.

In terms of legal framework, the Malaysian drug laws cover all aspects of drug-related offence, from prevention to rehabilitation. The five main drug laws enforced in Malaysia are (Pemadam, 2011):

- Dangerous Drugs Act 1952
- Poisons Act 1952
- Drug Dependants (Treatment and Rehabilitation) Act 1983, Amendment 1998
- Dangerous Drugs (Special Preventive Measures) Act 1985
- Dangerous Drugs (Forfeiture of Property) Act 1988

Malaysia strictly enforces its drug laws. Possession, use, and trafficking in illicit drugs in Malaysia are severe criminal offences. Malaysian legislation provides for a mandatory death penalty for

1 Introduction

convicted drug traffickers, with the best known case being the execution of two Australians for heroin smuggling in 1986 (Tempo, 1986). Other drug-related offenders can also expect heavy penalties such as long jail sentences and heavy fines.

1.10 Drug-related offence arrestment and seizures in Malaysia 2009

i). Arrestment of drug offenders

From January to December 2009, the Royal Malaysian Police (PDRM) and Royal Malaysian Custom (KDRM) have arrested 77,623 drug offenders under the Dangerous Drugs Act 1952 and Dangerous Drugs (Special Preventive Measures) Act 1985 (Adk, 2009). This figure is 18.99% higher than that arrested for the same period of time in 2008 (Table 1.1).

Table 1.1: Comparison of the total arrestment of drug offenders under the Dangerous Drug Act 1952 between 2008 and 2009

Type of offense	Jan-Dec 2009	Jan-Dec 2008	Difference 2009/2008
Dangerous Act 1952			
Section 39B	3,045	2,580	18.02%
Section 39A	5,538	4,870	13.72%
Other sections	66,540	56,593	17.58%
*ADB (LLPK) 1985	2,500	1,191	109.91%
Total	77,623	65,234	18.99%

*ADB (LLPK) 1985 = Dangerous Drug (Special Preventive Measures) Act 1985

Source: Agensi Antidadah Kebangsaan

1 Introduction

ii). Drug seizures

Meanwhile, different types of illicit drug have been seized by the three enforcing agents; PDRM, KDRM and the Pharmaceutical Services Division of the Malaysian Ministry of Health. Among the types of ATS seized, there was a drastic increase in the amount of Ecstasy powder and syabu, seized, while a marked drop in the amount seized for Ecstasy pills and Yaba pills (Table 1.2) (Adk, 2009).

Table 1.2: Comparison of ATS seized between 2008 and 2009

Drug type	Jan-Dec 2009	Jan-Dec 2008	Difference 2009/2008
Ecstasy powder (kg)	708.52	8.6	8,136.60%
Syabu (kg)	1,159.66	356.92	224.91%
Ecstasy (pills)	75,515	80,778	-6.51%
Yaba (pills)	107,952	281,343	-61.63%

Source: Agensi Antidadah Kebangsaan

Under the Dangerous Drugs (Forfeiture of Property) Act 1988, the PDRM has handled a total of 2,341 cases of property seizures in 2009. Based on the numbers recorded, there is an increase of 120 cases (5.4%) in 2009 compared with 2008 (Table 1.3) (Adk, 2009).

Table 1.3: Comparison of property seized under Property Forfeiture Act 1988 between 2008 and 2009

Property seizure	Jan-Dec 2009	Jan-Dec 2008	Difference 2009/2008
Total number of cases	2,341	2,221	5.40%
Value of property confiscated	38,200,000	70,300,000	84.03%

1 Introduction

1.11 Demographic of drug users in Malaysia 2009

According to the latest report from the Malaysian National Drug Information System (NADI) (Adk, 2009), in which statistics of drugs users in Malaysia were gathered from January to December 2009, there was an increase in the number of drug users detected. The number increased from 12,352 for the same period of time in 2008 to 15,736 drug users in 2009 (a 27.40% increment).

Among the number of cases identified, 7,123 were new users, indicating an increment of 19.94% compared to 5,939 for the same period of time in 2008. The number of repeat offenders detected were as many as 8,613, an increment of 34.31% compared with the same period of time in 2008 (6,413) (Table 1.4).

Table 1.4: Comparison of drug users identified between 2008 and 2009

Case status	Jan-Dec 2009	Percentage	Jan-Dec 2008	Difference 2009/2008
New user*	7,123	45.27%	5,939	19.94%
Repeat user**	8,613	54.73%	6,413	34.31%
Total	15,736	100.00%	12,352	27.40%

*Detected for the first time by NADI.

**Previously detected by NADI.

i). Comparison by state

Amongst all the states, Penang recorded the highest number of detected drug users at 2,255, followed by Kedah (2,016), Kelantan (1,902), Selangor (1,864) and Kuala Lumpur (1,635). Compared to

1 Introduction

January-December 2008, all states recorded an increase in number of detected drug users except for Kuala Lumpur, Terengganu, Perak, Malacca and Sabah in 2009.

ii). **Comparison by ethnicity**

Amongst drug users detected between January-December 2009, the majority were of Malay ethnics (13,705 or 87.09%), which is 0.16% of the total Malay population in Malaysia (8,826,000) (Table 1.5).

Table 1.5: Comparison of drug users identified by ethnic between 2008 and 2009

Ethnic	Jan-Dec 2009	Percentage	Jan-Dec 2008	Difference 2009/2008
Foreigner	4	0.03%	12	-66.67%
Sarawak pribumi	23	0.15%	17	35.29%
Sabah pribumi	56	0.36%	150	-62.67%
Indian	942	5.99%	1,090	-13.58%
Chinese	951	6.04%	1,438	-33.87%
Malay	13,705	87.09%	9,562	43.33%
Others	55	0.35%	83	-33.73%
Total	15,736	100.00%	12,352	27.40

iii). **Comparison by gender**

Of the 15,736 drug users detected in 2009, as many as 15,458 were male (98.23%) and 278 female (1.77%), reflecting an increment of 28.01% and 0.72% in male and female users, respectively, compared with figure recorded for January-December 2008.

1 Introduction

iv). **Comparison by age group**

Data gathered over the 12 month periods also showed that youth population aged between 19-39 years old continue to be major drug users (11,949). Of all drug users identified, 332 (2.15%) are in fact teenagers (13-18 years old). The 25-29 year old users remain to be the biggest group of drug user (22.08%). Of particular note, there was an alarming 327% increase from 11 in 2008 to 47 in 2009 in users aged between 13-15 years old.

v). **Comparison by occupation**

The report also indicates that majority of the drug users are employed (15,123 or 96.10%). It was noted that general labourers constitute the biggest drug abuse population (7,280 or 46.26%), followed by employees in the industries of servicing (29.25%), construction (6.20%), technical (4.87%) and farming/fishing (4.82%).

vi). **Comparison by level of education**

The majority of drug users (10,711 or 65.55%) received minimum Form 3 secondary education, of which 4,197 (28.78%) attained SRP/LCE/PMR academic qualification. There was an increase in the number of drug users with STP/HSC/STPM and university degree qualification.

vii). **Comparison by reasons of starting drug abuse**

As in the past years, the main reason of starting drug abuse is due to influence from friends (66.27%), for pleasure (12.47%) and out of

1 Introduction

curiosity (11.37%). Other reasons include stress, pain relieve purpose, and inadvertent usage.

viii). **Comparison by types of drug used**

Marijuana abuse recorded the highest percentage (33.09%) over the 12 months in 2009, while 1,298 or 8.24% were detected to take ATS, which includes Ecstasy pills, methamphetamine (syabu) and amphetamine (Table 1.6).

1 Introduction

Table 1.6: Comparison of drug users identified by types of drug between 2008 and 2009

Drug type	Jan-Dec 2009	Percentage	Jan-Dec 2008	Difference 2009/2008
<u>Opiates</u>				
Heroin	5,047	32.07%	4,974	1.47%
Morphine	3,386	21.52%	3,640	-6.98%
Codeine/cough syrup	50	0.32%	70	-28.57%
Opium	5	0.03%	9	-44.44%
<u>Marijuana</u>				
Cannabis	5,207	33.09%	1,726	201.68%
Psychotropic pills	39	0.25%	145	-73.10%
<u>ATS</u>				
Ecstasy pills/MDMA	83	0.53%	119	-30.25%
Metamphetamine (syabu)	1,131	7.19%	1,443	-21.62%
Amphetamine	84	0.53%	225	-62.67%
<u>Inhalant</u>				
Gum	0	0.00%	1	-100.00%
Others	704	4.47%	0	0.00%
Total	15,736	100.00%	12,352	27.40%

1 Introduction

ix). **Comparison by types of drug used by ethnic**

Amongst the Malay drug users, the three most common drugs used are heroin (29.94%), morphine (21.10%) and methamphetamine (7.07%).

As for Chinese drug users, the three most common drugs used are heroin (45.32%), morphine (26.71%) and methamphetamine (10.83%).

When a comparison is made between all ethnics, Malay drug users are the largest cannabis users (93.03%), followed by Indians (4.32%) and Chinese (2.17%). Similarly, the majority of ATS users are Malay, followed by Chinese and Indians (Table 1.7).

Table 1.7: Comparison of ATS users identified by ethnic and types of drug abuse

Drug type/ethnic	Ecstasy/MDMA		Methamphetamine		Amphetamine	
Malay	66	79.52%	969	85.68%	75	89.29%
Chinese	14	16.87%	103	9.11%	6	7.14%
Indian	2	2.41%	27	2.39%	3	1.50%
Sabah	0	0.00%	22	1.95%	0	0.00%
Sarawak	1	1.20%	5	0.44%	0	0.00%
Others	0	0.00%	5	0.44%	0	0.00%
Foreigners	0	0.00%	0	0.00%	0	0.00%
Total	83	100.00%	1,131	100.00%	84	100.00%

1 Introduction

1.12 Problems associated with ATS or general drug abuse

An increasing use of ATSs has been identified in the past decades and become an epidemic in many parts of the world.

i). Social consequences

The social consequences of drug abuse can be seen in several areas, with the most prominent impact on family, health, and crime. According to a 2004 research on the socio-economic impact of ATS in New Zealand (Wilkins *et al.*, 2004), it was reported that about one third of those who had used an ATS drug in the last year reported experiencing harm in at least one area of their lives from the use of these drug types. About half of the frequent methamphetamine users reported harm in the areas of friendship and social life (55%), health (55%), and energy and vitality (53%). Work and work opportunities were also rated as seriously affected by frequent methamphetamine users.

ii). Family and community

ATS abuse is frequently associated with family and social problems. The disintegration of many families, for example, has been correlated more strongly with drug abuse than with poverty (Unodc, 1998a). On the other hand, the increasing use of heroin and psychotropic substances may be due in part to the breakdown of traditional family structures and values (Singhanetra-Renard, 1993). Young people are also more vulnerable than older people to the negative consequences of drug use, particularly in areas such as educational achievement and employment (Wilkins *et al.*, 2004).

1 Introduction

iii). Health

Methamphetamine consumption is constantly linked to high-risk HIV behaviours (Semple et al., 2004, Reback et al., 2004, Urbina and Jones, 2004, Kurtz and Inciardi, 2003) and more recently, cardiovascular problems (Perez *et al.*, 1999, Kaye *et al.*, 2007, Droogmans *et al.*, 2007, De Silva *et al.*, 2007). The most serious problem, however, reported by frequent methamphetamine users was psychological rather than physical. About two-thirds of frequent methamphetamine users reported anxiety, mood swings, short temper, paranoia and depression, while 21% of them reported suicidal thoughts and 13% suicide attempts after using the drug (Wilkins *et al.*, 2004).

As a potent psychostimulant with a high dependence liability, methamphetamine abuse is closely associated with the risk of acute and chronic psychological disturbance, including psychosis (Who, 1997).

iv). Crime

Frequent methamphetamine users were often involved in other illegal activities.

In the 2004 report of the socio-economic impact of ATS in New Zealand (Wilkins *et al.*, 2004), one third of the frequent methamphetamine users had sold methamphetamine, and about 40% had earned income from illegal activities in the last 6 months, with drug

1 Introduction

dealing the most common type of illegal activity. Heavy drug users tend to resort to selling drug as a way to support their own consumption.

More recently, amphetamine use has also been associated with increased crime and violence (e.g. feuds between trafficking gangs, robbery, homicide) (Kosten and Singha, 1999). Compared with other psychoactive drugs, chronic amphetamine use is more closely related to violent behaviour.

Locally, in 2009 alone the Malaysian police have arrested 77,663 people due to drug related offences, including those with positive urine test for ATS (Adk, 2009).

v). Economic consequences

On individual basis, the increasing trend in methamphetamine use raises particular concern because of its deleterious effects on individuals and related health costs. The health costs of a drug addict have been reported to be almost 80% higher than those of an average citizen (Unodc, 1998b).

On a bigger scope, illicit drug use and trafficking also poses a significant impact on the economic sectors in consumer countries. Important and valuable resources are sacrificed, diverting from legitimate and more sustainable investments to drug production and consumption, which in turn impacts negatively on the productivity of the users (Unodc, 1998b).

1 Introduction

Drug abuse also raises the GDP, the largest part of which is used for drug-related crime and law enforcement costs (Unodc, 1998b). For instance, the Malaysian government has to spend more than RM300 million each year in its endeavour against illicit drug activities, half of which are used to set up rehabilitation centres (Utusan, 2006).

As regards to finance, two significant consequences of illicit drug-associated problem are money laundering and criminal investment (Unodc, 1998b).

1.13 Medical complications of ATS abuse

Amphetamines have mood-altering properties, which can occur in both short and long term use, and thus significant behavioural effects on the users.

i). Short-term effects of ATS

As mentioned, ATSs are addictive stimulants of the central nervous system (CNS). Use of ATS leads to various clinical effects: euphoria, intensifying emotions, altering self-esteem, and increasing alertness, aggression, and sexual appetite (Richards *et al.*, 2009).

While changes in mood, excitation, motor movements, sensory perception, and appetite are mediated more directly by central dopaminergic alterations, alterations in serotonin level are postulated to be the cause of amphetamine-related mood changes, psychotic behaviour and aggressiveness (Richards *et al.*, 2009).

1 Introduction

Therefore, immediately after taking methamphetamine, users experience a “rush” or “high” caused by the increased levels of dopamine and serotonin. The users’ sensation of pleasure and well-being is intensified, and they reported of a sense of euphoria, heightened level of alertness and increased energy (Volkow *et al.*, 1999). Users also experience increased libido and enhanced sexual pleasure, which is why methamphetamine use is associated with high-risk sexual behaviour (e.g. unprotected sexual intercourse, multiple sex partners) (Shoptaw, 2006, Mmwr, 2006). These drug effects may last up to 12 hours (Anonymous, 2004).

As the drug effects wear off, the users come down from the “high” and start to experience symptoms such as anxiety, insomnia and paranoia (Gard, 2004). Some users may exhibit violent behaviour, while some experience hallucinations (Gard, 2004). Table 1.8 lists some of the signs indicating that a person might be using methamphetamine.

Table 1.8: Signs indicating a person might be using methamphetamine

- | |
|--|
| <ul style="list-style-type: none">• Decreased appetite• Anorexia• Episodes of sudden and violent behaviour• Paranoia, hallucinations• Insomnia• Compulsive cleaning and grooming• Confusion• Scratching• Tremors |
|--|

(Gard, 2004)

1 Introduction

Short-term methamphetamine use has also been reported to increase heart rate, blood pressure, temperature and rate of breathing, constriction of blood vessels, and cardiac arrhythmia (Maxwell, 2005).

ii). Long-term effects of ATS

Long-term abuse of ATS causes many negative health effects that may be difficult or impossible to reverse.

First of all, distinctive changes occur in the physical appearance of long-term methamphetamine users, producing an aging effect (Winslow *et al.*, 2007). These changes usually result from malnutrition, severe dental decay, poor hygiene and weight loss. Long-term users of methamphetamine often exhibit skin-picking behaviours, which can lead to abscesses (Lee *et al.*, 2005).

As a consequence of dopamine depletion due to chronic use of ATS, potentially irreversible neuronal changes can occur and that result in neurological and psychiatric symptoms (Volkow *et al.*, 2001, Sekine *et al.*, 2003). Neurotoxic effects of chronic ATS use include neurochemical alterations in areas of the brain associated with learning, thus leading to cognitive impairment and behavioural deficits (Maxwell, 2005). Long-term ATS users have also showed signs of memory loss that is similar to Alzheimer's disease (Gard, 2004).

And certainly, long-term abuse results in addiction, which is almost impossible for user to quit without medical treatment.

1 Introduction

Another significant consequence of chronic (or high-dose) ATS abuse is the development of psychosis. In particular, the Methamphetamine Treatment Project in California (Zweben *et al.*, 2004) found participants had high levels of psychiatric symptoms, namely depression and attempted suicide, as well as anxiety and psychotic symptoms. They also reported high incidence of anger-control problem and violent behaviour, which corresponded with a high prevalence of assault and weapon charges.

iii). **Withdrawal syndrome**

Following cessation of chronic ATS use, users experience withdrawal syndrome, characterised by depression, psychomotor agitation, sleep disturbance (rebound REM with disturbing vivid dreams), and fatigue accompanied by dysphoria, irritability, anhedonia, anxiety, hyperphagia and intense drug craving (Kosten and Singha, 1999, McGregor *et al.*, 2005). In some respects it resembles an atypical depression.

While the withdrawal was previously divided into 'crash', 'withdraw' and 'extinction' - more recent studies suggest a more gradual improvement in mood and functioning over a 3-4 week period (Lago and Kosten, 1994).

In fact, a study by McGregor *et al* (McGregor *et al.*, 2005) showed that methamphetamine withdrawal syndrome can be categorized into two phases:

1 Introduction

- An acute phase lasting 7-10 days following cessation of dependent use, during which overall symptom severity declined in a linear pattern from a high initial peak.
- A sub-acute phase lasting at least 2 weeks following the end of the acute phase during which most withdrawal symptoms remained relatively mild and stable.

During the acute phase, it was noted that patients had increased sleeping and eating, depression-related symptoms and, less severely, anxiety and craving-related symptoms.

Oversleeping was obvious during the acute phase, but was not followed by a period of insomnia during the sub-acute phase. Certainly, patients who had been using methamphetamine for a longer period of time had a more severe withdrawal course.

1.14 Effects on other areas of health

Besides impacting the central nervous systems, long-term use of ATSS has been associated with clinical toxicities on cardiovascular system and respiratory systems, poorer cognitive functioning and mental health, as well as other severe health problems.

i). Cardiovascular system

Methamphetamine users are at elevated risk of cardiac pathology. Cardiovascular symptoms, including chest pain, ischemia, myocardial infarction, tachycardia and palpitations (Richards *et al.*, 2009), are

1 Introduction

common in ATS abuse. Cases of stroke have also been reported with the use of ATS (Perez et al., 1999).

ii). Respiratory system

Like cocaine abusers, many ATS abuse patients present to emergency departments with respiratory symptoms (Albertson *et al.*, 1995, Derlet *et al.*, 1989). Respiratory signs commonly associated with ATS use include dyspnea and wheezing (Richards *et al.*, 2009). Pulmonary hypertension has also long been reported in methamphetamine users (Arnett *et al.*, 1976, Lewman, 1972). The variability of symptoms seems to depend on the type of ATS used, the dosage and route of administration.

iii). Infectious diseases

Intravenous methamphetamine use has been related to the risk of a number of sexually-transmitted and blood-borne infectious diseases, such as endocarditis (Cooper *et al.*, 2007), viral hepatitis (Gonzales *et al.*, 2006), and human immunodeficiency virus (HIV) disease (Colfax *et al.*, 2004, Shoptaw *et al.*, 2002). In HIV-infected patients, methamphetamine abuse can further lead to medical complications including hypertension, hyperthermia, rhabdomyolysis and stroke (Urbina and Jones, 2004).

iv). Effects on pregnancy and foetus

Methamphetamine use during pregnancy can be dangerous to both the mother and the foetus.

1 Introduction

While methamphetamine abuse during pregnancy has been associated with maternal deaths (Catanzarite and Stein, 1995, Stewart and Meeker, 1997), which result in spontaneous abortion or teratogenesis to the foetus, methamphetamine exposure throughout gestation has been related with decreased growth in infants, even if they were exposed only for the first two trimesters (Smith *et al.*, 2003). In one study (Oro and Dixon, 1987), it was found that infants exposed to methamphetamine throughout gestation were significantly smaller for gestational age compared with the unexposed group. In addition, 49% of them exhibited withdrawal signs, including abnormal sleep patterns, poor feeding, tremors and hypertonia. However, only 4% required medications.

Other foetal effects associated with methamphetamine exposure include intrauterine growth retardation, prematurity, clefting, cardiac anomalies and death (Wouldes *et al.*, 2004, Stewart and Meeker, 1997).

v). Effects on children and adolescents

Limited evidence suggests that children may be at risk developmentally due to both the direct effects of prenatal drug exposure. Academic and mild physical delays were noted in a 14-year follow-up study of children born to women who abused amphetamines during pregnancy, though other potential confounders might be present (Cernerud *et al.*, 1996).

Children who are exposed to methamphetamine environmentally (e.g. methamphetamine laboratories) may experience headaches, nausea,

1 Introduction

dizziness, dyspnea, chest pain, eye irritation and burns (Ndcip, 2007). Beyond clinical effects, these children are at risk for inadvertent poisoning, trauma, neglect, abuse and adverse psychological effects (Horton *et al.*, 2003, Kolečki, 1998, Swetlow, 2003).

vi). Other effects on health

- Effects on skin

The most common dermatological manifestations in patients who abuse amphetamine-related compounds are probably related to self-induced skin picking, intravenous needles, or burns (Cadier and Clarke, 1993).

- Hepatotoxicity

Hepatocellular damage has been reported after both acute and chronic amphetamine abuse (Kamijo *et al.*, 2002, Henry *et al.*, 1992, Jones *et al.*, 1994).

- Effects on gastrointestinal system

Abuse of methamphetamine has been associated with the formation of giant gastrointestinal ulcers and ischemic colitis (Jones *et al.*, 1994, Johnson and Berenson, 1991).

- Impact on dental health

Patients taking amphetamines are also at increased risk of gingival enlargement (Hasan and Ciancio, 2004), rampant caries, enamel erosion, xerostomia, bruxism and muscle trismus (Rhodus and Little,

1 Introduction

2005). Table 1.9 below summarizes the major signs and symptoms of ATS toxicity (Albertson *et al.*, 1999).

Table 1.9: Major signs and symptoms of ATS toxicity

Cardiac	Psychiatric
Chest pain	Anxiety
Myocardial infarction	Depression
Palpitations	Paranoia
Arrhythmia	Delirium/hallucination
Cardiomyopathy	Psychosis
Myocarditis	Suicide
Hypertension	Aggressive behaviour
Sudden death	Euphoria/hyperactivity
Valve thickening	Irritability
Neurologic	Respiratory
Headache	Pulmonary oedema
Seizure	Dyspnea
Cerebral infarcts/stroke	Bronchitis
Cerebral vasculitis	Pulmonary hypertension
Mydriasis	Haemoptysis
Cerebral haemorrhage	Pleuritic chest pain
Subarachnoid	Asthma exacerbation
Intraventricular, Intracerebral	Pulmonary granuloma
Others	
Ulcers	Anorexia/weight loss
Hyperoxia	Rhabdomyolysis
Renal failure	Nausea/vomiting
Ischaemic colitis	Disseminated vasculitis
Obstetric complications	

Chapter TWO: Psychiatric Co-morbidity and Suicidality in Methamphetamine Dependence

2.1 Abstract

Introduction: In the past decade, psychiatric related disorders or sequelae in methamphetamine users started to receive more attention. It has been demonstrated that there is an increased rate of attempted suicide in this population. Previous studies suggested that one of the predictors for suicide attempts in methamphetamine users is psychiatric co-morbidity mainly depressive symptoms.

Objectives: To determine the prevalence of suicidality and prevalence psychiatric co-morbidity in methamphetamine dependence patients. We also wanted to determine the association between psychiatric co-morbidity and suicidality.

Methodology:

Design : This was a cross sectional study.

Setting: The study was conducted at outpatient psychiatric clinic, Department of Psychological Medicine, University Malaya Medical Centre (UMMC), Kuala Lumpur and at Drug Rehabilitation Centre Papar, Sabah

Patients: Study population were methamphetamine dependence and the eligibility criteria were patients aged more than 18 and meeting the DSM-IV criteria for methamphetamine dependence.

Measures: The Mini International Neuropsychiatric Interview

2 Psychiatric Co-morbidity and Suicidality

(M.I.N.I.) and a structured questionnaire to assess: (i) sociodemographic background (ii) psychiatric co-morbidity in Axis I psychiatric disorders and (iii) drug use history.

Results: The subjects had high co-morbid rates for psychiatric illnesses. Of the 305 subjects, 54.4% of the subjects had at least one non-substance use axis I psychiatric disorder. The most frequently diagnosed co-morbidity was antisocial personality disorder (32.1%). The prevalence of suicidality was 12.1 % (37/305). Major depressive disorder, panic disorder, current and lifetime psychotic disorder were associated with suicidality. After multiple logistic regression, the independent risk factors of suicidality were major depression (OR 7.3; 95% C.I.: 3.0, 17.8) and lifetime psychotic disorder (OR 5.1; 95% C.I.: 1.3, 20.3).

Conclusion: The prevalence of psychiatric co-morbidity and suicidality is high in this population. We feel that identification and treatment of co-morbid psychiatric illnesses in this population is of utmost importance.

Keywords: Methamphetamine dependence, Psychiatric co-morbidity, Suicidality, Psychosis, Anti-social personality, Depression, Association study, Prevalence.

2 Psychiatric Co-morbidity and Suicidality

2.2 Introduction

2.2.1. Psychiatry Co-morbidity

The term 'comorbidity' was introduced in medicine by Feinstein to denote those cases in which a 'distinct additional clinical entity' occurred during the clinical course of a patient having an index disease (Feinstein, 1970). This term could indicate not only those cases in which a patient receives both a psychiatric and a general medical diagnosis (e.g. schizophrenia and diabetes mellitus), but also those cases in which a patient receives two or more psychiatric diagnoses (e.g. major depression and substance dependence). The co-occurrence of psychiatric disorder and substance dependence disorder is a common condition (Wilson, 2007). The presence of a psychiatric disorder increases the risk for the presence of substance dependence disorder and vice-versa (Swendsen *et al.*, 2010). Much evidence suggest that when these disorders occur together, is associated with worse health outcomes, more complex clinical management, and increased health care costs (Wilson, 2007).

To help explain this co-morbidity, we need to first recognize that substance dependence is a mental illness. It is a complex brain disease characterized by compulsive, at times uncontrollable drug craving, seeking, and uses despite devastating consequences (Leshner, 1999). Behaviors that stem from drug-induced changes in brain structure and function through complex neuroadaptive process. This process guides behaviour in maladaptive directions during which severe physical and social consequences engulf and disable the addict

2 Psychiatric Co-morbidity and Suicidality

(White, 2002). These changes occur in some of the same brain areas that are disrupted in other mental disorders, such as depression, anxiety, or schizophrenia. It is therefore not surprising that population surveys show a high rate of co-occurrence, or co-morbidity, between substance dependence and other mental illnesses (Regier *et al.*, 1990). It is often difficult to disentangle the overlapping symptoms of drug addiction and other mental illnesses, making diagnosis and treatment complex. Correct diagnosis is critical to ensuring appropriate and effective treatment. Ignorance of or failure to treat a co-morbid disorder can jeopardize a patient's chance of recovery.

2.2.2. Methamphetamine Dependence

According to the definition in DSM-IV (Apa, 1994), dependence is measured by three or more of the following criteria, occurring at any time in the same 12 month period:

1. Tolerance, as defined by either:

- (a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect; or
- (b) A markedly diminished effect with continued use of the same amount of the substance.

2. Withdrawal, as manifested by either of the following:

- (a) A characteristic withdrawal syndrome; or
- (b) The same or closely related substance is used to relieve or avoid withdrawal symptoms.

2 Psychiatric Co-morbidity and Suicidality

3. The substance is taken in larger amounts or for a longer period than intended.

4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.

5. A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects.

6. Important social, occupational or recreational activities are reduced or given up because of substance use.

7. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. Degree and severity of dependence is primarily influenced by:

(a) The type and potency of methamphetamine being used. The use of crystal methamphetamine ('ice' or 'shabu'), which is usually more potent, may lead to dependence more quickly than methamphetamine base or powder; or

(b) The mode of administration. Injecting methamphetamine may lead to higher levels of dependence than with other forms of administration such as snorting or ingesting.

The widespread abuse of methamphetamine impacts society at various levels; from the individual, to the individual's family and to their community. Methamphetamine dependence gives rise to serious behavioural, medical and psychiatric consequences, imposing an immense burden on the medical, public health and criminal justice

2 Psychiatric Co-morbidity and Suicidality

systems due to increased legal problems, violence, and high rates of HIV infection and hepatitis due to high risk sexual behaviour (Hando and Hall, 1994).

2.2.3. Epidemiology of Methamphetamine dependence in Malaysia

In Malaysia, within the first three months of 2010, the National Anti-Drug Agency has identified 3,611 drug addicts, which is an increase of about 110% for the same period in the previous year. Among these identified addicts, 18% were dependent on amphetamine-type-stimulants (ATS), which include amphetamine, methamphetamine and ecstasy pills. This represents a 117% increase in ATS addicts compared with the same period in the previous year.(Kdn, 2010) In the year 2008 there were 1,443 methamphetamine dependence subjects in Malaysia, while in the year 2009 there were 1,131 methamphetamine dependence subjects identified (Adk, 2009).

2.2.4. Methamphetamine Dependence, Psychiatry Co-Morbidity and Suicidality

Although there has been a marked worldwide increase in methamphetamine dependence, the psychiatric sequelae of methamphetamine dependence has not been well described. It is only in the past decade has psychiatric related disorders or sequelae in methamphetamine users started to receive more descriptive attention. The majority of methamphetamine users have been shown to suffer from a lifetime history of depression (Zweben *et al.*, 2004, Hall *et al.*, 1996). Not surprisingly, it has been demonstrated that there is an

2 Psychiatric Co-morbidity and Suicidality

increase rate of attempted suicide in this population. One of the predictors for suicide attempts in methamphetamine users is depressive symptoms (Zweben *et al.*, 2004). Studies have also shown suicide attempts were aggravated in patients with substance-use co-morbidity when compared with those without (Glasner-Edwards *et al.*, 2008a). Besides mood symptoms, chronic or heavy methamphetamine users may exhibit psychotic symptoms that resemble paranoid schizophrenia (Glasner-Edwards *et al.*, 2008a). However data on methamphetamine-related anxiety disorders on the other hand is still scarce and the association between anxiety symptoms and substance use remains controversial (Yen and Chong, 2006).

In Malaysia, the prevalence of psychiatric sequelae of methamphetamine abuse as well as the association between the psychological effects of methamphetamine and suicidality is yet to be established. Having such data in hand will aid in formulating more cost-effective treatments for methamphetamine dependent users and in the prevention of social problems, such as suicidal attempts.

2 Psychiatric Co-morbidity and Suicidality

2.2.5. RESEARCH QUESTION

- i). What was the prevalence of psychiatric co-morbidity among methamphetamine dependence patient?
- ii). Has psychiatric co-morbidity associated with suicidality among methamphetamine dependence patients?

2.2.6. STUDY OBJECTIVES

i). Primary Objective

- To determine the prevalence of psychiatric co-morbidity among methamphetamine dependent Malaysians who seek treatment.
- To determine the prevalence of suicidality in methamphetamine dependence patients.

ii). Secondary objective

To determine the association between psychiatric co-morbidity and suicidality among methamphetamine dependence patients.

2.2.7. HYPOTHESIS

There is association between psychiatric co-morbidity and suicidality among methamphetamine dependence patients.

2.3 Methodology

2.3.1. Study design

This study was a hospital-based and drug rehabilitation-based cross sectional study.

2 Psychiatric Co-morbidity and Suicidality

2.3.2. Setting and study period

The study was conducted at outpatient psychiatric clinic, Department of Psychological Medicine, University Malaya Medical Centre(UMMC), Kuala Lumpur and at Drug Rehabilitation Centre Papar, Sabah from June 2008 until June 2009.

2.3.3. Study population

Study population were methamphetamine dependence and the eligibility criteria were patients aged more than 18 and meeting the DSM-IV criteria for methamphetamine dependence.

2.3.4. Sample size and sampling procedure

Sample size was calculated using the computer software EPI-INFO. Universal sampling was used for the recruitment of the study subjects.

- i.) The power of the study was taken at 80% level.
- ii.) The significance level of the statistic tests done was at 95% Confidence Interval level and α was set at 0.05. The Null hypothesis was rejected when $p < 0.05$.
- iii.) The Odds Ratio was taken at 2.1 for the calculation.
- iv.) Expected frequency of disease in unexposed group (The proportion of the population with suicidality without depression - 55%)(Glasner-Edwards *et al.*, 2008b).
- v.) The ratio of case to control was taken as 1 : 1.

Total number of samples = 274 patients

2 Psychiatric Co-morbidity and Suicidality

2.3.5. Study variables

Dependent variable

Suicidality

Independent variables

Sociodemographic variables

- i). Age
- ii). Sex
- iii). Current employment status
- iv). Total family income
- v). Educational level
- vi). Marital status

Psychiatric Co-morbidity in Axis I psychiatric disorders

- i). Mood disorders
- ii). Anxiety disorders
- iii). Psychotic disorder
- iv). Alcohol dependence
- v). Alcohol abuse
- vi). Poly-substance use
- vii). Antisocial personality disorder

2 Psychiatric Co-morbidity and Suicidality

- viii). Present of any psychiatric co-morbidity

Drug use history variables

- i). Age of first substance use
- ii). Duration of drug use
- iii). Amount of money spend on drug per month
- iv). Route of administration of methamphetamine
- v). Criminal record
- vi). Lifetime prevalence of substance use

2.3.6. Operational definitions

The operational definitions for variables and scale were described in detail in ANNEX “A”.

2.3.7. Study instrument

The Mini International Neuropsychiatric Interview (M.I.N.I.) is a short structured diagnostic interview for DSM-IV or ICD-10 psychiatric disorders for the Major Axis I psychiatric disorder including suicidality (Sheehan *et al.*, 1998b). It has been widely used in international clinical trials and epidemiological studies.(Joling *et al.*, 2008, Van't Veer-Tazelaar *et al.*, 2009) The M.I.N.I. was available in local language (Sheehan *et al.*, 1998a).

2.3.8. Data collection methods

2 Psychiatric Co-morbidity and Suicidality

All patients with drug dependence were approached during the study period. Patients were briefed on the study and written consent was obtained. Only patients with urine toxicology screened positive for methamphetamine and within 30 days of last use of the methamphetamine were included in the study. A face-to-face interview was conducted using a structured questionnaire on drug use behaviour and the Mini International Neuropsychiatric Interview (M.I.N.I.). The interviews were conducted by a qualified psychiatrist.

The structured questionnaire for drug use behaviour was used to assess severity of illicit drug addiction. This questionnaire consisted of three sections: (i) sociodemographic background (ii) psychiatric co-morbidity in Axis I psychiatric disorders and (iii) drug use history

2.3.9. Data Management

The data were checked before ending each interview session and before compilation to ensure completeness. Raw data obtained were coded and entered into Statistical Package for Social Sciences (SPSS) Version 16.0. The data were summarized by running frequency distributions and simple descriptive statistics (means and standard deviations). Cleaning for double entry and outliers were done before the analysis.

2.3.10. Data analysis

i). Univariate analyses

2 Psychiatric Co-morbidity and Suicidality

Only one independent variable was analyzed at a time. It allowed the researcher to describe the characteristics of the study subjects. No comparisons were made at this point. For nominal independent variables, they were described in the form of frequencies and percentages. For continuous independent variables, they were summarized and described as means, standard deviations and median.

ii). Bivariate analysis

Pearson's Chi-square test and Simple Logistic Regression were used to determine the possible association of significant variables to the occurrence of suicidality by determining the Odds ratio and 95% Confidence Interval. Continuous data were analyzed using the t-test. Skewed data was analysed using non parametric test. Subsequently the continuous variables were recategorised and further tested by Pearson's Chi-square test and Simple Logistic Regression. An alpha level of significance 0.05 was set for all analyses. Significant risk factors in the bivariate analysis were partially adjusted with other significant variables to take care of interactions and confounding effects.

iii). Multiple logistic regression

After partial adjustment, all significant independent variables were further analyzed with enter, forward stepwise, backward stepwise methods of multiple logistic regression to determine which risk factors independently act as predictors of suicidality.

2 Psychiatric Co-morbidity and Suicidality

2.3.11. Pre-test

A pre-test of the questionnaires was done on 5 patients who were attending the psychiatric clinic, UMMC. These respondents were excluded from the study. Some corrections were made after the pre-test to facilitate patients' understanding of the questionnaires.

2.3.12. Ethical consideration

Ethical approval was obtained from Medical Ethics Committee of UMMC. Before any interview, patients were informed regarding the nature and purpose of the study and the respondents were given the assurance that all information given will be treated with confidentiality. A written consent was obtained from the patients prior the interviews.

2 Psychiatric Co-morbidity and Suicidality

2.4 Results

Demographics

305 subjects were enrolled in this study and the prevalence of suicidality was 12.1%(37/305). Table 2.1 displayed the socio demographic characteristics of the study population. Majority of the study subjects was male, single and has fulltime job. There was no association between socio demographic variables and suicidality.

Psychiatric Comorbidity

The subjects had high comorbid rates for psychiatric illnesses. Of the 305 subjects, 54.4% of the subjects had at least one non-substance use axis I psychiatric disorder. The most frequently diagnosed comorbidity was antisocial personality disorder (32.1%). Major depressive disorder, schizophrenia, panic disorder, current and lifetime psychotic disorder were associated with suicidality. For substance use axis I psychiatric disorder, poly-substance use has the highest prevalence (60.3%) and it was associated with suicidality (OR, 3.1; 95%CI.: 1.3,7.4)(Table 2.2).

Drug Use History

Table 2.3 showed the results for methamphetamine use patterns and drug use history. Mean age at first methamphetamine use was 23.9 ± 8.8 years and mean duration of methamphetamine use was 6.4 ± 4.9 years. The most common route of administration of methamphetamine was smoking (68.2%). In addition to methamphetamine, the most frequently used illicit drug was cannabis. Cigarette smoking and

2 Psychiatric Co-morbidity and Suicidality

alcohol consumption were also very common among the study subjects.

After multiple logistic regression, the independent risk factors of suicidality were major depression (OR 7.3; 95% C.I.: 3.0, 17.8) and lifetime psychotic disorder (OR 5.1;95% C.I.: 1.3, 20.3)(Table 2.4).

2 Psychiatric Co-morbidity and Suicidality

Table 2.1: Association between Demographic Characteristics and Suicidality among Methamphetamine Dependence

Variables	Suicidality	No suicidality	Total n=305	OR(95%CI)
Age (years), mean \pm SD	30.3 \pm 8.0	32.2 \pm 9.2	30.5 \pm 8.2	-1.9(-4.8,0.9)*
Gender				
‡Male n (%)	37(12.3)	265(87.7)	302	
Female n (%)	1(33.3)	2(66.7)	3	3.6(0.3,40.5)
Education				
Primary n (%)	3(5.8)	49(94.2)	52	0.9(0.1,5.6)
Secondary n (%)	33(14.9)	189(85.1)	222	2.5(0.6,11.1)
‡Tertiary n (%)	2(6.5)	29(93.5)	31	
Employment				
‡Fulltime n (%)	31(13.0)	208(87.0)	239	
Part-time n (%)	3(7.7)	36(92.3)	39	0.6(0.2,1.9)
Student n (%)	2(5.3)	4(66.7)	6	3.4(0.6,19.1)
Unemployed n (%)	2(9.5)	19(90.5)	21	0.7(0.2,3.2)
Total Income (RM), mean + SD	n=38 2460.5 \pm 3037.9	n=264 2216 \pm 6365.8	n=302 2247.4 \pm 6045.5	-283.8(-2311.2, 1823.6)* ¶
Marital Status				
‡ Married n (%)	13(12.3)	93(87.7)	106	
Single n (%)	23(13.3)	150(86.7)	173	1.1(0.5,2.3)
Divorced & widow n (%)	1(3.8)	25(96.2)	26	0.3(0.04,2.3)

*mean difference(95% CI of Difference)

‡reference group

¶Mann-Whitney U Test

2 Psychiatric Co-morbidity and Suicidality

Table 2.2: Association between Axis I Psychiatric Disorders and Suicidality among Methamphetamine Dependence

Psychiatric Co-morbidity	Suicidality n (%)	No suicidality n (%)	Total n=305(%)	OR(95%CI)
Mood Disorders				
Major depressive disorder*	23 (42.6)	31 (57.4)	54 (17.7)	12.5(5.8-26.9)
Bipolar Disorder (Mania)	9(18.0)	41(82.0)	50 (16.4)	1.7(0.7-4.0)
Anxiety Disorders				
Generalized Anxiety disorder	1(50.0)	1(50.0)	2 (0.7)	7.4(0.4-121.1)
Obsessive compulsive disorder	0(0)	3(100)	3 (1.0)	0.9(0.9- 1.0)
Panic disorder*	5(35.7)	9(64.3)	14 (4.6)	4.4(1.4-14.1)
Social phobia	2(22.2)	7(77.8)	9 (3.0)	2.1(0.4-10.6)
Psychotic disorder				
Schizophrenia*	5(55.5)	4(44.5)	9(3.0)	10.3(2.6-40.3)
Current*	15(30.6)	34(69.4)	49 (16.1)	4.6(2.2-9.9)
Lifetime*	34(22.2)	119(77.8)	153 (50.2)	14.1(4.2-47.3)
Alcohol dependence	14(17.7)	65(82.3)	79 (25.9)	1.9(0.9-3.9)
Alcohol abuse	9(15.3)	50(84.7)	59 (19.3)	1.4(0.6-3.1)
Poly-substance use*	30(16.3)	154(83.7)	184 (60.3)	3.1(1.3-7.4)
Antisocial personality disorder	17(17.2)	82(82.8)	98 (32.1)	1.9(0.9-3.8)
Any psychiatric co-morbidity*	35(21.1)	131(78.9)	166(54.4)	18.3(4.3-77.6)

*statistically significant $p < 0.05$

2 Psychiatric Co-morbidity and Suicidality

Table 2.3: Association between Drug Use History and Suicidality among Methamphetamine Dependence

Variables	Suicidality	No suicidality	Total	mean difference (95% CI of difference)
Age of first substance use Year (mean \pm SD)				
Methamphetamine n=304	24.11 \pm 7.95	23.84 \pm 8.90	23.88 \pm 8.78	-0.27(-3.30,2.78)¶
Alcohol n=192	18.81 \pm 7.75	19.13 \pm 5.79	19.09 \pm 6.08	0.32(-2.18,2.82)
Cannabis n=104	17.57 \pm 4.62	18.86 \pm 5.21	18.68 \pm 5.13	1.28(-1.64,4.21) ¶
Nicotine n=293	15.77 \pm 5.46	16.15 \pm 5.42	16.10 \pm 5.42	0.38(-1.55,2.30)
Heroin n=35	21.00 \pm 4.90	23.63 \pm 5.02	23.03 \pm 5.05	2.63(-1.46,6.72)
Duration of drug use Year (mean \pm SD)				
Methamphetamine*	7.86 \pm 4.98	6.24 \pm 4.92	6.44 \pm 4.94	-1.62(-3.32,0.08) ¶
Alcohol	11.16 \pm 24.52	5.24 \pm 6.72	5.96 \pm 10.71	-5.92(-9.57,-2.28) ¶
Cannabis	2.70 \pm 4.87	2.45 \pm 5.08	2.48 \pm 5.04	-0.25(-2.00,1.49)
Nicotine	14.73 \pm 8.93	12.17 \pm 7.28	12.48 \pm 7.52	-2.56(-5.15,0.03)
Heroin	2.68 \pm 6.36	1.15 \pm 4.18	1.34 \pm 4.51	-1.53(-3.08,0.03)
Amount of money spend on drugs,RM** (mean \pm SD)				
Methamphetamine*	1585.14 \pm 1574.58	883.37 \pm 1611.69	968.78 \pm 1621.03	-701.77(-1256.61,-146.92) ¶
Alcohol	270.81 \pm 614.58	187.37 \pm 408.85	197.52 \pm 438.59	-83.44(-234.80,69.92) ¶
Cannabis	73.24 \pm 180.09	74.87 \pm 261.44	74.67 \pm 252.70	1.66(-85.75,89.00) ¶
Nicotine	138.65 \pm 111.53	154.89 \pm 384.85	152.91 \pm 362.70	16.24(-109.15,141.63) ¶
Heroin*	289.19 \pm 682.64	56.20 \pm 266.05	84.65 \pm 351.42	-232.99(-351.62,-114.35) ¶
Route of administration of methamphetamine				
‡Oral n(%)	1(5.6)	17(94.4)	18 (5.9)	
Nasal n(%)	7(9.2)	69(90.8)	76(25.0)	1.7(0.2,14.9)§
Smoking n(%)	28(13.5)	179(86.5)	207(68.2)	2.7(0.3,20.7) §
Injection n(%)	1(33.3)	2(66.7)	3 (0.9)	8.5(0.4,195.5) §
Criminal record				
Illegal activity n(%)	18(12.6)	125(87.4)	143 (47.0)	1.1(0.5,2.1) §
Conviction n(%)	20(13.3)	130(86.7)	150 (49.3)	1.2(0.6,2.5) §
Lifetime prevalence of substance use				
Alcohol n(%)			192 (62.9)	
Cannabis n(%)			104 (34.1)	
Nicotine n(%)			293 (96.1)	
Heroin n(%)			35 (11.5)	
Glue n(%)			25 (8.2)	
Ketamine n(%)			7 (2.3)	

*statistically significant
**Ringgit Malaysia

‡reference group

¶Mann-Whitney U Test
§ Odds Ratio(95%CI)

2 Psychiatric Co-morbidity and Suicidality

Table 2.4: Independent Predictors for Suicidality among Methamphetamine Dependence Patient

Psychiatric co-morbidity	Odds ratio	95% CI
Major depression	7.3	3.0,17.8
Psychotic disorder lifetime	5.1	1.3,20.3

Adjusted with age, sex and marital status

2 Psychiatric Co-morbidity and Suicidality

2.5 Discussion

Our study demonstrated that methamphetamine dependence in Malaysians who seek treatment have high psychiatric comorbidity, with antisocial personality disorder being the most prevalently diagnosed comorbidity. Psychiatric comorbidities that were significantly associated to suicidality in the treatment-seeking methamphetamine users were depression, schizophrenia, panic disorder, and current and lifetime psychotic disorder.

The observations from our study supported findings of earlier studies that methamphetamine-dependent individuals are at greater risk of experiencing particular psychiatric symptoms (Kalechstein *et al.*, 2000, Yen and Chong, 2006, Chen *et al.*, 2003), and are more likely to experience depressive symptoms and suicidal ideation than the non-methamphetamine dependent individuals. The observation still holds even after adjusting for socio-demographic variables and dependence on other substances (Kalechstein *et al.*, 2000).

What remains uncertain at this point of time is whether psychiatric morbidity predisposes an individual to abuse drug, or drug use resulted in the psychiatric manifestations. A study by Yen and Chong (Yen and Chong, 2006) proposed that the psychiatric manifestations in methamphetamine users are very likely a result of stimulant use that has exceeded a certain threshold. Their study results are accordant to the findings of earlier studies, suggesting that the occurrence of psychiatric manifestations in methamphetamine-using individuals is not

2 Psychiatric Co-morbidity and Suicidality

correlated to lifetime-use duration or the amount consumed, but is more associated with increasing use of the stimulant.

Methamphetamine and Suicidality

Suicidality, or suicidal ideation, implicates an apparent risk for eventual suicide completion. The prevalence of methamphetamine-associated suicidality in our study was 12.1%, which is close to that reported in a study of adolescent methamphetamine users in Taiwan (Yen and Shieh, 2005).

In that study, a substantially higher percentage of adolescent methamphetamine users with suicidal ideation were diagnosed with depressive disorder, which is consistent with the findings of previous studies describing the association between depressive disorder and suicidal behaviour (Zweben *et al.*, 2004). That study also found that adolescent methamphetamine users with suicidal ideation were more likely to have a family history of substance abuse as compared with those without suicidal ideation. However, the family history of the methamphetamine dependents was not investigated in our study.

In order to identify the potential factors that precipitate the decision to commit suicide Callor (Callor *et al.*, 2005), conducted a study by examining medical examiner records of suicide completers. The study found that alcohol and methamphetamine were the most common substances detected in either blood or urine, or in both blood and urine of the youth suicide completers, whom at that point of time were not diagnosed for mental illness or not being non-compliant with

2 Psychiatric Co-morbidity and Suicidality

psychotropic medications. Similarly, in the Methamphetamine Treatment Project (Glasner-Edwards *et al.*, 2008b), it was found that psychiatric characteristics of methamphetamine users are strongly associated with substance abuse.

From these findings of our study and studies of other researchers, it is recommended that when treating methamphetamine-dependent individuals, a careful assessment of psychiatric history is warranted. In order to formulate an effective suicide prevention strategy, it is absolutely necessary to identify the risk factors for suicidal behaviour associated with methamphetamine abuse.

Methamphetamine and Depression

Our study shows that major depression (54% of total subjects) is a statistically significant independent risk factor for suicidality in methamphetamine-dependent users. Indeed, many studies have found a strong relationship between substance abuse and depression (Christie *et al.*, 1988, Deykin *et al.*, 1986, Kandel and Davies, 1986). For instance, Kalechstein *et al.* (Kalechstein *et al.*, 2000) reported that 57.1% of methamphetamine-dependent prison and jail inmates experienced depressive symptoms within the year prior to their study intake.

The prevalence of depression among methamphetamine users has been known to be higher than the general population, with the majority of methamphetamine users reporting a lifetime history of depression (Zweben *et al.*, 2004, Hall *et al.*, 1996). In addition, depressive

2 Psychiatric Co-morbidity and Suicidality

symptoms are also a major component of the withdrawal syndrome in the cessation of methamphetamine use (Markou and Kenny, 2002, McGregor *et al.*, 2005). Depressive symptoms can appear during immediate withdrawal and during the initial weeks and even months of abstinence following methamphetamine cessation (Rawson *et al.*, 2002a).

It remains unclear as to whether depressive symptoms preceded onset of drug use or methamphetamine use gave rise to depressive symptoms. This area of uncertainty underscores the need for further investigation. However, there are data (Peck *et al.*, 2005) to indicate that individuals felt depressed due to recent methamphetamine use, and less depressed if they had recently abstained. More importantly, the findings provide strong support for the potential of behavioural drug abuse treatments in attaining long-term reductions in depression and methamphetamine use in methamphetamine-dependent users.

Methamphetamine and Psychotic Disorder

In our study, 16.1% of subjects experienced current psychotic disorder while 50.2% have had lifetime psychotic disorder. This lifetime rate is higher compared with that reported in a study involving treatment-seeking methamphetamine-dependent gay and bisexual men, where 26.5% of them had lifetime histories of substance-induced psychotic disorders (Shoptaw *et al.*, 2003).

It is known that chronic or heavy methamphetamine use may induce psychotic symptoms that resemble paranoid schizophrenia. Such

2 Psychiatric Co-morbidity and Suicidality

symptoms include delusions, ideas of reference, and auditory hallucinations (Glasner-Edwards *et al.*, 2008a).

It is generally recognised that methamphetamine users with additional risk factors for psychotic illness, such as familial loading, may be at greater risk to develop psychotic symptoms. However, some individuals may experience symptoms for a considerably prolonged period, even in the absence of prior history of psychotic illness. Those symptoms could be an exacerbation of symptoms of an underlying psychotic illness (Curran *et al.*, 2004), or newly induced during intoxication and drug withdrawal (Zweben *et al.*, 2004).

The psychosis-inducing potential of methamphetamine is not unanticipated, considering that it is a more potent derivative of amphetamine, also a stimulant that is well-known to amphetamine-induced psychosis following chronic use (Chen *et al.*, 2003).

An earlier study by Chen *et al.* (Chen *et al.*, 2003) reported that among methamphetamine users, those with psychosis were more vulnerable to other psychiatric morbidities, which include major depressive disorder and anti-social personality disorder, when compared with those without psychosis. Our observation is in line with their findings, that is, methamphetamine-dependent individuals are highly associated with psychiatric co-morbidity. Therefore, careful screening and assessment of psychosis in methamphetamine-dependent users is essential in guiding effective treatment for this at-risk group.

2 Psychiatric Co-morbidity and Suicidality

Methamphetamine and Panic Disorder

Panic disorder was the prominent anxiety disorder reported in our subjects (4.6%). Data on methamphetamine-related panic disorder is scarce and the association between anxiety symptoms and substance use remains controversial (Yen and Chong, 2006).

One of the earlier reports linking methamphetamine and panic disorder was a case study of a young woman who had a relapse and worsening of panic disorder following a single injection of methamphetamine, despite after a long period of remission (Iwanami *et al.*, 1997). More recent data comes from the Methamphetamine Treatment Evaluation Study (MATES) (Cogger S, 2008), which is the first longitudinal treatment cohort study of methamphetamine-dependent users in Australia. Preliminary results from MATES showed that 31% of their sample subjects met the DSM-IV criteria for panic disorder (with or without Agoraphobia) in the past year.

Limitation and Errors

i). Adequacy of Sample Size

The required sample size was 274, when the calculated study sample was based on 80% power of the study and odds ratio 2.1 of bivariate association. The actual study has inflated the sample size to 305, in order to consider other important confounders would not have been missed during the development of the full model.

2 Psychiatric Co-morbidity and Suicidality

ii). Representative and Generalisation

The findings of this study could only generalize with caution because the study population was from the outpatient clinic located in a hospital in Kuala Lumpur and from one drug rehabilitation centre in Sabah. The study population differs from the patients in the community because of the treatment seeking behavior. Furthermore, there was ethnicity diversity in Sabah compared to other state in Malaysia. To make generalized inferences of the findings of this study to the methamphetamine dependence patients in community would be inappropriate because the setting in this study had introduced selection bias.

For a better generalization of the findings, it would be ideal to conduct a community survey. Unfortunately, such a study is not feasible to conduct due to the legal implication. The identified subjects would provide information bias, because they had offended the law and the possibility being charged to the court.

All identified patients were willing to be interviewed and consented to participate in this study.

iii). Instruments of the study

All the scales have been used widely in this country however until now, there has been no paper being published regarding the validation of the scales in the local population.

2 Psychiatric Co-morbidity and Suicidality

In view of the assessment of suicidality was through face-to-face interviewed using M.I.N.I., some of the patients might not have admitted that they ever had suicidality. This may introduce misclassification bias, between the presence and absence of suicidality among the methamphetamine dependent patient.

iv). Conduct of study

Information bias was one of the limitations especially when information was obtained via a face-to- face interview. The validity on history of drug use could be questioned, especially since some of the information could not be verified. Some of the information might occur long time ago and the possibility of recall bias could happen.

In some circumstances when a translator was needed, the translator may have misunderstood the questions even though further explanations were given and this led to the respondents providing the wrong answer.

v). Comparing findings with other studies

Comparison of the findings of this study to other studies may be inaccurate, although other studies examined the same variables, but the inclusion and exclusion criteria used to identify subjects or sampled population could differ, or study could be conducted with different study design.

Some similar confounder that has been examined by other studies, but slightly at different aspect was relationship. In this study, divorce has been identified as factor associated with suicidality, but in another

2 Psychiatric Co-morbidity and Suicidality

study, separation was highly associated with suicidality especially among youth (Wyder *et al.*, 2009). Other study has found women living with spouse and children as protective factor from suicide (Poudel-Tandukar *et al.*, 2010).

Some of the variables that have been included in other studies for the association of suicidality but not in this study were school performance as risk of suicide (Bjorkenstam *et al.*, 2010), acute stress reaction (Gradus *et al.*, 2010), genetic factor (Pregelj *et al.*, 2011), gun ownership (Kim *et al.*, 2011), environmental factors e.g. altitude (Kim *et al.*, 2011), temperature (Kim *et al.*, 2010b) and ambient particulate matter (Kim *et al.*, 2010a). Financial difficulties (Judd *et al.*, 2010) that lead to debt or due to gambling (Wong *et al.*, 2010) could be one of the reason for suicidality.

2.6 Conclusions

In conclusion, the prevalence of psychiatric comorbidity and suicidality is high in this population. We feel that identification and treatment of comorbid psychiatric illnesses in this population is of utmost importance, due to several reasons. Firstly, it is unethical not to screen and treat for psychiatric illnesses in this population, and untreated psychiatric illness cause unnecessary suffering. Failure to identify comorbid psychiatric illnesses here means an opportunity for treatment is lost in a population that is otherwise difficult to reach in the community. In the community, the drug user is said to be embedded in a web of psychological distortions and maladaptive behaviour that hinder compliance and entry into treatment. Denial, projection,

2 Psychiatric Co-morbidity and Suicidality

minimization, avoidance and omnipotence on the side of the drug user, and the negative effect they elicit and the counter transference on the side of the therapist may all hinder treatment in the community (Woody *et al.*, 1983). Secondly, identification and treatment of psychiatric illnesses must be addressed as the central role in relapse prevention of substance use. Comorbid psychiatric illnesses, particularly depression, are often associated with high rates of continued substance usage after treatment (Brewer *et al.*, 1998, Brooner *et al.*, 1997).

Chapter THREE: Prevalence and Association of Methamphetamine Induced-Psychosis

3.1 Abstract

Introduction: The use of methamphetamine in high dose produces a wide range of symptoms, including irritability, physical aggression, hyperawareness and psychomotor agitation. When used repeatedly and chronic, this stimulant can cause the most widely known side effect, which is drug-induced psychosis. It displays symptoms similar to those of paranoid schizophrenia, which is characterised by hallucinations, delusions and thought disorders.

Objectives: To determine the prevalence of methamphetamine induce psychosis and to determine the association between psychiatric co-morbidity and methamphetamine-induced psychosis.

Methodology:

Design : This was a cross sectional study.

Setting: The study was conducted at outpatient psychiatric clinic, Department of Psychological Medicine, University Malaya Medical Centre (UMMC), Kuala Lumpur and at Drug Rehabilitation Centre Papar, Sabah.

Patients: Study population were methamphetamine dependent and the eligibility criteria were patients aged more than

3 Methamphetamine Induced-Psychosis

18 and meeting the DSM-IV criteria for methamphetamine dependence. Those who had psychotic symptoms prior to methamphetamine dependence and those with a history of schizophrenia or other psychotic disorder were excluded.

Measures: The Mini International Neuropsychiatric Interview (M.I.N.I.) and a structured questionnaire to assess: (i) sociodemographic background (ii) psychiatric co-morbidity in Axis I psychiatric disorders and (iii) drug use history.

Results: The subjects had high rates for methamphetamine-induced psychosis. Of the 292 subjects, 47.9% of the subjects had at least one episode of psychotic symptoms after they were dependent on methamphetamine. About 13.0% of the patients were still having psychotic symptoms at the time of assessment. Persecutory delusion was the most common lifetime psychotic symptoms found in 101 participants (72.1%). Auditory hallucinations were the most common current psychotic symptoms found in 31 participants (81.6%). After multiple logistic regression, the independent risk factors of psychosis were bipolar disorder (OR 4.7; 95% C.I.: 1.4, 16.6), antisocial personality disorder (OR 3.7; 95% C.I.: 1.4, 9.8), higher amount of stimulant used and higher family income.

Conclusion: These findings substantiate the fact that methamphetamine users are highly associated with psychosis,

3 Methamphetamine Induced-Psychosis

including those without known history of schizophrenia or other psychotic disorders.

Keywords: Methamphetamine dependence, Psychiatric co-morbidity, Psychosis, Prevalence, Association study.

3 Methamphetamine Induced-Psychosis

3.2 Introduction

Methamphetamine is a derivative of amphetamine, with similar but more pronounced psychotropic properties (Nida, 1998). The use of methamphetamine produces a wide range of symptoms, including irritability, physical aggression, hyperawareness and psychomotor agitation.

When used in high dose or repeatedly, this stimulant can cause drug-induced psychosis that display symptoms similar to those of paranoid schizophrenia, which is characterised by hallucinations, delusions and thought disorders.

Methamphetamine-induced psychosis is one of the most widely known side effects associated with high-dose or chronic methamphetamine use (Griffith *et al.*, 1972, Hall *et al.*, 1996). In the Pacific region, especially Japan and Taiwan, psychosis as a result of methamphetamine abuse is common (Suwaki H. *et al.*, 2007, Chou *et al.*, 1999). In fact, earlier studies have reported that frequent methamphetamine use increases the risk of psychosis significantly, regardless of whether primary psychotic disorders, such as schizophrenia, are present in the patient (Mcketin *et al.*, 2006b, Chen *et al.*, 2003).

Other studies have also observed greater incidences of suicide attempts, hospitalisations and greater psychiatric symptom severity in patients with substance use comorbidity compared with those without substance use disorders (Drake *et al.*, 1996, Swofford *et al.*, 1996).

3 Methamphetamine Induced-Psychosis

In general, psychotic symptoms induced by substance use resolve within hours or days after withdrawal from the drug (transient type), but they may be significantly prolonged (persistent type) in some individuals, despite the absence of a known prior history of psychotic illness (Hall *et al.*, 1996, Iwanami *et al.*, 1994).

A drug-induced psychosis can be distinguished from primary psychotic disorders by the length of time the symptoms persist. In drug-induced psychosis, symptoms usually resolve after the drug is discontinued. If symptoms do not resolve within 2 weeks after cessation of substance use, a primary psychiatric disorder should be suspected (Larson, 2008).

In addition to the potential for methamphetamine use to induce psychosis, users with additional risk factors for psychotic illness (e.g. familial loading) may be particularly at greater risk of developing psychotic symptoms (Chen *et al.*, 2005). Those with psychotic disorders are also more likely to have other substance use disorders (Regier *et al.*, 1990).

An Australian study (Mcketin *et al.*, 2006b) have found that dependent methamphetamine users to be three times more likely to experience psychotic symptoms than their non-dependent counterparts, even after adjusting for history of schizophrenia and other psychotic disorders. This clearly shows that dependent methamphetamine users are a particularly high-risk group for psychosis.

3 Methamphetamine Induced-Psychosis

Despite the known risk for both drug-induced and drug-independent psychoses in methamphetamine users, there are limited number of studies on the prevalence of psychotic disorders and other associated factors in this population.

Methamphetamine abuse and its psychiatric sequelae are increasingly rampant in Malaysia. In Malaysia, within the first three months of 2010, the National Anti-Drug Agency has identified 3,611 drug addicts, which is an increase of about 110% for the same period in the previous year. Among these identified addicts, 18% were dependent on amphetamine-type-stimulants (ATS), which include amphetamine, methamphetamine and ecstasy pills. This represents a 117% increase in ATS addicts compared with the same period in the previous year (Kdn, 2010).

Before effective strategy and treatment plan can be devised to curb this public health and social burden of the country, an understanding of the demographic and characteristics of methamphetamine users is warranted. Therefore, the aims of this study were to investigate the prevalence of psychosis among methamphetamine-dependent patients and to investigate the associated factors.

3 Methamphetamine Induced-Psychosis

3.2.1. RESEARCH QUESTION

What factors associated with methamphetamine-induced psychosis?

3.2.2. STUDY OBJECTIVES

i). Primary Objective

To determine the prevalence of methamphetamine-induced psychosis.

ii). Secondary objective

To determine the association between psychiatric co-morbidity and methamphetamine-induced psychosis

3.2.3. HYPOTHESIS

There is association between psychiatric co-morbidity and methamphetamine-induced psychosis.

3.3 Methodology

3.3.1. Study design

This study was a hospital-based and drug rehabilitation-based cross sectional study.

3.3.2. Setting and study period

The study was conducted at outpatient psychiatric clinic, Department of Psychological Medicine, University Malaya Medical Centre(UMMC), Kuala Lumpur and at Drug Rehabilitation Centre Papar, Sabah from June 2008 until June 2009.

3 Methamphetamine Induced-Psychosis

3.3.3. Study population

Study population were methamphetamine dependence and the eligibility criteria were patients aged more than 18 and meeting the DSM-IV criteria for methamphetamine dependence. Those who had psychotic symptoms prior to methamphetamine dependence and those with history of schizophrenia or other psychotic disorders were excluded.

3.3.4. Sample size and sampling procedure

Sample size was calculated using the computer software EPI-INFO. Universal sampling was used for the recruitment of the study subjects.

- i.) The power of the study was taken at 80% level.
- ii.) The significance level of the statistic tests done was at 95% Confidence Interval level and α was set at 0.05. The Null hypothesis was rejected when $p < 0.05$.
- iii.) The odds Ratio was taken at 2.0 for the calculation.
- iv.) Expected frequency of disease in unexposed group (The proportion of the population with psychosis without psychiatric comorbidity - 21%) (Mcketin *et al.*, 2006b)
- v.) The ratio of case to control was taken as 1 : 1.

Total number of samples = 290 patients

3 Methamphetamine Induced-Psychosis

3.3.5. Study variables

Dependent variable

Methamphetamine induce psychosis

Independent variables

Sociodemographic variables

- i). Age
- ii). Sex
- iii). Current employment status
- iv). Total family income
- v). Educational level
- vi). Marital status
- vii). Past medical history

Psychiatric Co-morbidity in Axis I psychiatric disorders

- i). Mood disorders
- ii). Anxiety disorders
- iii). Suicidality
- iv). Alcohol dependence
- v). Alcohol abuse
- vi). Poly-substance use
- vii). Antisocial personality disorder
- viii). Present of any psychiatric co-morbidity

3 Methamphetamine Induced-Psychosis

Drug use history variables

- i). Age of first substance use
- ii). Duration of drug use
- iii). Amount of money spend on drug per month
- iv). Route of administration of methamphetamine
- v). Criminal record
- vi). Lifetime prevalence of substance use

3.3.6. Operational definitions

The operational definitions for variables and scale were described in detail in ANNEX “A”.

3.3.7. Study instrument

The M.I.N.I. is a short structured diagnostic interview for DSM-IV or ICD-10 psychiatric disorders for the Major Axis I psychiatric disorder (Sheehan *et al.*, 1998b). It has been widely used in international clinical trials and epidemiological studies (Joling *et al.*, 2008, Van't Veer-Tazelaar *et al.*, 2009). The MINI was available in local language (Sheehan *et al.*, 1998a).

3.3.8. Data collection methods

All patients with drug dependence were approached during the study period. Patients were briefed on the study and written consent was obtained. Only patients with urine toxicology screened positive for methamphetamine and within 30 days of last use of the

3 Methamphetamine Induced-Psychosis

methamphetamine were included in the study. A face-to-face interview was conducted using a structured questionnaire on drug use behaviour and the Mini International Neuropsychiatric Interview (M.I.N.I.). The interviews were conducted by a qualified psychiatrist.

The structured questionnaire for drug use behaviour was used to assess severity of illicit drug addiction. This questionnaire consisted of three sections: (i) sociodemographic background (ii) psychiatric co-morbidity in Axis I psychiatric disorders and (iii) drug use history

3.3.9. Data Management

The data were checked before ending each interview session and before compilation to ensure completeness. Raw data obtained were coded and entered into Statistical Package for Social Sciences (SPSS) Version 16.0. The data were summarized by running frequency distributions and simple descriptive statistics (means and standard deviations). Cleaning for double entry and outliers were done before the analysis.

3.3.10. Data analysis

i). Univariate analyses

Only one independent variable was analyzed at a time. It allowed the researcher to describe the characteristics of the study subjects. No comparisons were made at this point. For nominal independent variables, they were described in the form of frequencies and percentages. For continuous independent variables, they were

3 Methamphetamine Induced-Psychosis

summarized and described as means, standard deviations and median.

ii). **Bivariate analysis**

Pearson's Chi-square test and Simple Logistic Regression were used to determine the possible association of significant variables to the occurrence of methamphetamine induced psychosis by determining the Odds ratio and 95% Confidence Interval. Continuous data were analyzed using the t-test. Skewed data was analysed using non parametric test. Subsequently the continuous variables were re-categorised and further tested by Pearson's Chi-square test and Simple Logistic Regression. An alpha level of significance 0.05 was set for all analyses. Significant risk factors in the bivariate analysis were partially adjusted with other significant variables to take care of interactions and confounding effects.

iii). **Multiple logistic regression**

After partial adjustment, all significant independent variables were further analyzed with enter, forward stepwise, backward stepwise methods of multiple logistic regression to determine which risk factors independently act as predictors of methamphetamine induced psychosis.

3.3.11. **Pre-test**

A pre-test of the questionnaires was done on 5 patients who were attending the psychiatric clinic, UMMC. These respondents were

3 Methamphetamine Induced-Psychosis

excluded from the study. Some corrections were made after the pre-test to facilitate patients' understanding of the questionnaires.

3.3.12. Ethical consideration

Ethical approval was obtained from Medical Ethics Committee of UMMC. Before any interview, patients were informed regarding the nature and purpose of the study and the respondents were given the assurance that all information given will be treated with confidentiality. A written consent was obtained from the patients prior the interviews.

3.4 Results

Demographics

Two hundred ninety two subjects were enrolled in this study. Of the 292 subjects, 140 (47.9%) of the subjects had at least one episode of psychotic symptoms after they were dependent on methamphetamine. 38 (13.0%) of the patients were still having psychotic symptoms at the time of assessment. Table 3.1 displayed the socio demographic characteristics of the study population. Participants had a mean age of 30.5 ± 8.2 years. Majority of the study subjects was male (98.9%). Participants with psychotic symptoms were 2 times more likely to be single (OR 1.9; 95% C.I.: 1.2, 3.1) and 3 times more likely to be unemployed (OR 3.3; 95% C.I.: 1.2, 9.4). There was statistically significant association between total income and psychosis. Those who had psychotic symptoms had higher income than those without psychotic symptoms (Table 3.1).

Psychotic Symptoms

Table 3.2 showed the prevalence rates of lifetime and current psychotic symptoms elicited by the use of MINI among the methamphetamine induce psychosis. Persecutory delusion (72.1%) was the most common symptom found during lifetime among the participants followed by strange or unusual belief (69.3%) and auditory hallucinations (60.7%). For those who still having current psychotic symptoms, auditory hallucinations was the most common (81.6%), followed by persecutory delusions (76.3%) and delusions of reference (71.7%) (Table 3.2).

3 Methamphetamine Induced-Psychosis

Psychiatric Comorbidity

Table 3.3 compared the participants with psychosis and without psychosis regarding diagnostic comorbidity. Those in the psychosis group were more likely to have a diagnosis of panic disorder (92.3% vs 7.7%), bipolar mania (87% vs 13%), antisocial personality disorder (81.9% vs 18.1%), major depressive disorder (77.6% vs 22.4%) and alcohol dependence (62.3% vs 37.7%). Not surprisingly, the substance-induced psychotic group had higher rates of poly-substance use (62.8% vs 37.2%).

Drug Use History

Table 3.4 showed the results for methamphetamine use patterns and drug use history. The occurrence of psychotic symptoms was significantly associated with mean duration of methamphetamine use. Those who had psychosis used methamphetamine over longer duration (7.6 ± 5.1 years) compared to those who do not have psychotic symptoms (5.3 ± 4.5 years). The amount of money spent per month to buy methamphetamine was also statistically significantly higher among those who experienced psychotic symptoms compared to those who do not have psychotic symptoms. The mean amount spend for those who had psychotic symptoms were RM 1,560.60 \pm 2,063.30 per month, while those who do not have psychotic symptoms only spend RM 376.90 \pm 557.40.

After multiple logistic regression, the independent risk factors of psychosis were mania (OR 4.7; 95% C.I.: 1.4, 16.6), antisocial

3 Methamphetamine Induced-Psychosis

personality disorder (OR 3.7; 95% C.I.: 1.4, 9.8), higher amount of stimulant use and higher family income (Table 3.5).

3 Methamphetamine Induced-Psychosis

Table 3.1: Association between Demographic Characteristics and Psychosis among Methamphetamine Dependence Patients

Variables	Psychosis	No Psychosis	Total n=292	OR(95%CI)
Age (years), mean \pm SD	30.5 \pm 8.4	30.5 \pm 7.9	30.5 \pm 8.2	*-0.2 (-2.1, 1.6)
Gender				
‡Male n (%)	137 (47.4)	152 (52.6)	289	
Female n (%)	3 (100)	0 (0)	3	
Education				
Primary n (%)	20 (40.0)	30 (60.0)	50	0.7 (0.3, 1.5)
Secondary n (%)	102 (48.3)	109 (51.7)	211	0.5 (0.2, 1.4)
‡Tertiary n (%)	18 (58.1)	13 (41.9)	31	
Employment				
‡Fulltime n (%)	108 (47.0)	122 (53.0)	230	
Part-time n (%)	12 (33.3)	24 (66.7)	36	0.6 (0.3, 1.3)
Student n (%)	5 (83.3)	1 (16.7)	6	5.2 (0.6, 45.2)
Unemployed n (%)**	15 (75.0)	5 (25.0)	20	3.3 (1.2, 9.4)
Total Income (RM), mean + SD	n = 138 2950.7 \pm 8424.8	n = 151 1544.1 \pm 1169.1	n=290 2247.4 \pm 6045.5	* ¶ -1406.5 (-2768.7, -44.4)
Marital Status				
‡ Married n (%)	38 (36.9)	65 (63.1)	103	
Single n (%)**	87 (55.5)	76 (44.5)	163	1.9 (1.2, 3.1)
Divorced & widow n (%)	15 (57.7)	11 (42.3)	26	2.0 (0.8, 4.9)

** statistically significant

*mean difference(95% CI of Difference)

‡reference group

¶Mann-Whitney U Test

3 Methamphetamine Induced-Psychosis

Table 3.2: Clinical Symptom Profiles of Patients with Methamphetamine Psychosis (Elicited By the Use of MINI)

Psychotic Symptoms	Lifetime (%)	Current (%)
Any psychotic symptoms	140 (100)	38 (100)
Persecutory delusions	101 (72.1)	29 (76.3)
Strange or Unusual Beliefs	97 (69.3)	21 (55.3)
Auditory hallucinations	85 (60.7)	31 (81.6)
Thought Insertion	78 (55.7)	24 (63.1)
Thought reading	63 (45.0)	17 (44.7)
Delusions of references	46 (32.8)	27 (71.1)
Visual hallucinations	22 (15.7)	11 (28.9)
Disorganized speech		8 (21.1)
Negative psychotic symptoms		6 (15.8)
Disorganized behaviour		2 (5.3)

3 Methamphetamine Induced-Psychosis

Table 3.3: Association between Axis I Psychiatric Disorders and Psychosis among Methamphetamine Dependence Patients

Psychiatric Co-morbidity	Psychosis n (%)	No Psychosis n (%)	Total n=292 (%)	OR(95%CI)
Mood Disorders				
Major depressive disorder*	38 (77.6)	11 (22.4)	49 (16.7)	4.8 (2.3, 9.8)
Bipolar Disorder (Mania)*	40 (87.0)	6 (13.0)	46 (15.7)	9.7 (3.9, 23.8)
Anxiety Disorders				
Generalized Anxiety disorder	0 (0)	2 (100)	2 (0.7)	
Obsessive compulsive disorder	2 (66.7)	1 (33.3)	3 (1.0)	2 (0.2, 22.2)
Panic disorder*	12 (92.3)	1 (7.7)	13 (4.5)	14.3 (1.8, 111.2)
Social phobia	5 (55.6)	4 (44.4)	9 (3.0)	1.4 (0.3, 5.2)
Suicidality*	28 (90.3)	3 (9.7)	31 (10.6)	12.4 (3.7, 41.9)
Alcohol dependence*	48 (62.3)	29 (37.7)	77 (26.3)	2.2 (1.3, 3.7)
Alcohol abuse	33 (61.1)	21 (38.9)	54 (18.5)	1.9 (1.0, 3.5)
Poly-substance use*	108 (62.8)	64 (37.2)	172 (58.9)	4.6 (2.8, 7.7)
Antisocial personality disorder*	77 (81.9)	17 (18.1)	94 (32.2)	9.7 (5.3, 17.7)
Any psychiatric co-morbidity*	115 (75.2)	38 (24.8)	153(52.4)	13.8 (7.8, 24.3)

*statistically significant

3 Methamphetamine Induced-Psychosis

Table 3.4: Association between Drug Use History and Psychosis among Methamphetamine Dependence Patients

Variables	Psychosis	No Psychosis	Total	mean difference (95% CI of difference)
Age of first substance use				
Year (mean \pm SD)				
Methamphetamine n=292	22.9 \pm 8.2	24.8 \pm 9.2	23.8 \pm 8.8	1.9 (-0.1, 3.9) ¶
Alcohol n=180	18.5 \pm 5.6	19.7 \pm 6.5	19.1 \pm 5.9	1.2 (-0.5, 2.9)
Cannabis n=95	18.6 \pm 5.0	18.8 \pm 5.6	18.6 \pm 5.2	0.2 (-2.1, 2.6) ¶
Nicotine n=272	15.6 \pm 4.9	16.5 \pm 5.7	16.1 \pm 5.4	0.9 (-0.3, 2.2)
Heroin n=35	22.4 \pm 4.8	25.2 \pm 5.5	23.0 \pm 5.0	2.8 (-1.2, 6.9)
Duration of drug use				
Year (mean \pm SD)				
Methamphetamine*	7.6 \pm 5.1	5.3 \pm 4.5	6.4 \pm 4.9	-2.3 (-3.4, -1.2) ¶
Alcohol	6.8 \pm 13.6	5.0 \pm 6.5	5.9 \pm 10.7	-1.8 (-4.2, 0.6) ¶
Cannabis*	3.9 \pm 6.0	0.9 \pm 3.2	2.3 \pm 4.9	-2.9 (-4.0, -1.8)
Nicotine	12.6 \pm 7.9	12.3 \pm 7.1	12.4 \pm 7.5	-0.3 (-2.0, 1.3)
Heroin*	2.0 \pm 5.6	0.6 \pm 2.8	1.4 \pm 4.6	-1.4 (-2.4, -0.4)
Amount of money spend on drugs, RM** (mean \pm SD)				
Methamphetamine*	1560.6 \pm 2063.3	376.9 \pm 557.4	986.8 \pm 1650.0	-1183.6 (-1524.7, -842.4) ¶
Alcohol	225.1 \pm 507.5	169.9 \pm 356.2	198.3 \pm 440.4	-55.2 (-154.2, 43.7) ¶
Cannabis*	123.3 \pm 336.3	25.9 \pm 101.3	72.5 \pm 252.2	-97.3 (-153.4, -41.3) ¶
Nicotine	184.2 \pm 494.8	121.5 \pm 130.7	154.0 \pm 369.4	-62.6 (-144.3, 19.0) ¶
Heroin*	184.2 \pm 494.8	121.5 \pm 130.7	81.6 \pm 340.6	-102.5 (-181.3, -23.8) ¶
Route of administration of methamphetamine				
‡Oral n(%)	10 (55.6)	8 (44.4)	18 (5.9)	
Nasal n(%)	37 (50.6)	36 (49.3)	73 (25.0)	0.9 (0.3, 2.6) §
Smoking n(%)	89 (45.4)	107 (54.6)	196 (67.1)	0.7 (0.2, 1.9) §
Injection n(%)	2 (66.7)	1 (33.3)	3 (1)	1.6 (0.1, 20.9) §
Criminal record				
Illegal activity n(%)	69 (51.1)	66 (48.9)	135 (46.2)	1.2 (0.8, 2.0) §
Conviction n(%)	77 (52.7)	69 (47.3)	146 (50.0)	1.5 (0.9, 2.3) §
Lifetime prevalence of substance use				
Alcohol n(%)			180 (61.6)	
Cannabis n(%)			95 (32.5)	
Nicotine n(%)			272 (93.1)	
Heroin n(%)			35 (11.9)	
Glue n(%)			20 (6.8)	
Ketamine n(%)			7 (2.4)	
*Statistically Significant	§Odds Ratio(95%CI)			
‡Reference Group	**Ringgit Malaysia			
¶Mann-Whitney U Test				

3 Methamphetamine Induced-Psychosis

Table 3.5: Independent Predictors for Psychosis Among Methamphetamine Dependence Patients

	Odds Ratio	95% CI
Bipolar Mania	4.7	1.4, 16.6
Antisocial Personality	3.7	1.4, 9.8
Amount of Stimulant Used	1.0	1.0, 1.2
Higher Family Income	1.0	1.0, 1.1

Adjusted with age and sex

3.5 Discussion

This is the first study in Malaysia to examine the prevalence of methamphetamine induced psychosis among methamphetamine dependent from hospital-based and drug rehabilitation-based populations.

In comparison with other studies, the prevalence rate of current or past psychotic disorders found in this investigation is substantially higher than those reported in other settings. The Methamphetamine Treatment Project (Glasner-Edwards *et al.*, 2008a) reported a 12.9% prevalence rate of current or past psychotic disorders among treatment-seeking, methamphetamine-dependent adults, while a study involving methamphetamine-dependent gay and bisexual men seeking outpatient drug abuse treatment noted 26.5% of prevalence. (Shoptaw *et al.*, 2003) A study of inpatients admitted for substance dependence in Sweden showed that 31.5% of methamphetamine abusers met criteria for psychotic diagnoses. (Dalmau *et al.*, 1999)

However in a cross-country study including Australia, Japan, Philippines and Thailand where psychotic symptoms in methamphetamine psychotic in-patients were evaluated using the Mini-International Neuropsychiatric Interview found high prevalence rate of lifetime and current psychotic symptoms (Srisurapanont *et al.*, 2003). 74.4% out of 130 participants were having persecutory delusions followed by auditory hallucinations, strange and unusual beliefs and thought reading during their lifetime. They also found that 44.6% of the

3 Methamphetamine Induced-Psychosis

participants were having current psychotic symptoms of auditory hallucination.

The clinical symptoms profiles of patients with methamphetamine psychosis were almost similar between our study and other studies (Srisurapanont et al., 2003, Chen et al., 2003). In all the studies, the main psychotic symptoms were persecutory delusions and auditory hallucinations.

A study in Taiwan (Chen et al., 2003) showed that when compared with methamphetamine users without psychosis, methamphetamine users with psychosis were younger when they first used methamphetamine, used larger amounts of the drug, had educational levels of high school or lower. The majority of their subjects were single, divorced, separated or widowed. The demographic characteristics of our study subjects were similar to those reported in their study, where the majority of our patients were young adults, male, single, and most of them received up to secondary education only. In addition, we further found that psychosis among methamphetamine dependent users was 3 times more prevalent in those who were unemployed (OR 3.3) and 2 times more common in those who were single (OR 1.9).

The majority of our study subjects were male in both psychosis and no-psychosis groups reflects the fact that substance use and substance use disorders are more common among men, both in the general population and in the population with severe mental illness.

3 Methamphetamine Induced-Psychosis

In our study, methamphetamine-dependent users who had psychosis were generally, though not statistically significantly, younger when they first used the substance, as compared with methamphetamine-dependent users who did not develop psychosis (22.9 years vs 24.8 years). Those who developed psychotic disorders, however, were statistically significantly using methamphetamine over a longer period of time (7.6 years) compared to those who are not psychotic (5.3 years). Psychosis was also associated with longer duration of using cannabis and longer duration of using heroin.

This makes it reasonable to assume that methamphetamine users who started using the drug at a younger age tend to use the drug for a longer time and at higher risk of developing psychotic illnesses. This may imply a dose-response relationship in the development of methamphetamine induced psychosis. This relationship was previously observed in association between cannabis and psychosis (Linszen *et al.*, 1994).

Those who had psychosis tend to make higher total family income than those were not psychotic (RM2,950.7 vs RM1,544.1), may explain why methamphetamine-dependent subjects with psychosis spent significantly higher amounts of money on the stimulant drug than their non-psychotic counterparts (RM1,560.6 vs RM376.9). The psychosis group also spent significantly more money on cannabis and heroin.

Methamphetamine users not only are a high-risk population for drug-induced psychosis, but are also at risk of suffering from other

3 Methamphetamine Induced-Psychosis

psychiatric co-morbidities. Our study demonstrated that methamphetamine-dependent subjects with psychotic symptoms had significantly higher prevalence than the non-psychotic methamphetamine users in several of the Axis I psychiatric disorders assessed: bipolar mania (87% vs 13%; OR 9.7), major depression (77.6% vs 22.4%; OR 4.8), panic disorder (92.3% vs 7.7%; OR 14.3), anti-social personality disorder (81.9% vs 18.1%; OR 9.7) and alcohol dependence (62.3% vs 37.7%; OR 2.2).

Substance use in patients with bipolar disorder is common. The National Epidemiological Catchment Area Study (ECA) found a 56% lifetime prevalence of substance abuse or dependence among persons with bipolar disorder (Regier et al., 1990). Estroff et al (1985) found that the reported lifetime prevalence of amphetamine abuse in bipolar disorder subject was 38.8% (Estroff et al., 1985). Although the frequency of this co-occurrence is well-documented, the reasons for this association are not clear. There are several potential hypotheses for why substance use and bipolar disorders co-occur: (a) substance abuse occurs as a symptom of bipolar disorder; (b) substance abuse is an attempt by bipolar patients to self-medicate symptoms; (c) substance abuse causes bipolar disorder; and (d) substance use and bipolar disorders share a common risk factor (Strakowski and Delbello, 2000).

Some of our findings concur with the results found in a study by Chen et al (Chen et al., 2003), where their methamphetamine-induced psychosis patients had significantly higher prevalence of major

3 Methamphetamine Induced-Psychosis

depression (OR 7.4), alcohol dependence (OR 3.4), and antisocial personality disorder (OR 3.3), when compared with their non-psychotic counterparts.

The risk of suicidality was also considerably elevated in methamphetamine users with psychosis than those without psychosis (OR 12.4) in our study. Comparable findings were reported in a study by Caton and colleagues (Caton *et al.*, 2005), where individuals with substance-induced psychosis had higher rates of suicidal idea in the previous year. Their study also found that substance-induced psychosis subjects had higher rates of polysubstance use (alcohol, cocaine, heroin, hallucinogen and polydrug). As shown in our study, alcohol dependence, alcohol abuse and lifetime history of polysubstance use were significantly associated with psychotic symptoms among methamphetamine-dependent subjects. The most frequently used illicit drug besides methamphetamine in this study was cannabis and heroin.

Studies have shown that combined abuse of methamphetamine and alcohol can aggravate mental disorders (Yamamura *et al.*, 1991, Chen *et al.*, 2003) because concomitant use of these substances increases toxicity in methamphetamine users, thereby increasing the risk of methamphetamine psychosis. Interaction of amphetamine and alcohol has been reported to increase toxicity in humans and animals (Yamamura *et al.*, 1991, Yamamura *et al.*, 1992). These observations support the significant association between alcohol dependence and methamphetamine psychosis observed in this study.

3 Methamphetamine Induced-Psychosis

After performing multiple logistic regression analysis to eliminate the confounding effect, the independent predictors for psychosis found in this study were bipolar mania, major depression, antisocial personality, single marital status, spent significantly larger amount of money to buy methamphetamine, and having a higher total family income.

The demographic data and clinical characteristics of methamphetamine-induced psychosis individuals as well as the key predictors derived from this study will provide important insights into substance-induced psychosis, and will impart a clearer understanding of the relationship of substance use and substance use disorders to psychotic illnesses. We also believe that this information will be of great help to the relevant authorities to formulate effective treatment and management of severe and persistent mental illnesses that co-occur with substance use.

Limitation and Errors

i). Adequacy of Sample Size

The required sample size was 290, when the calculated study sample was based on 80% power of the study and odds ratio 2.0 of bivariate association. The actual study subjects were 292 and have maintained the power of study.

ii). Representative and Generalisation

The findings of this study could only generalize with caution because the study population was from the outpatient clinic located in a hospital

3 Methamphetamine Induced-Psychosis

in Kuala Lumpur and from one drug rehabilitation centre in Sabah. The study population differs from the patients in the community because of the treatment seeking behavior. Furthermore, there was ethnicity diversity in Sabah compare to other state in Malaysia. To make generalized inferences of the findings of this study to the methamphetamine dependence patients in community would be inappropriate because the setting in this study had introduced selection bias.

For a better generalization of the findings, it would be ideal to conduct a community survey. Unfortunately, such a study is not feasible to conduct due to the legal implication.

All identified patients willing to be interviewed and consented to participate in this study.

iii). Instruments of the study

All the scales have been used widely in this country however until now, there was no paper being published regarding the validation of the scales in the local population.

iv). Conduct of study

Information bias was one of the limitations especially when information was obtained via a face-to- face interview. The validity on history of drug use could be questioned, especially some of the information could not be verified. Some of the information might occur long time ago and the possibility of recall bias could happen.

3 Methamphetamine Induced-Psychosis

In some circumstances when a translator was needed, the translator may have misunderstood the questions even though further explanations were given and this led to the respondents providing the wrong answer.

v). Comparing Findings With Other Studies

Comparison of the findings of this study to other studies may be inaccurate, although other studies examined the same variables, but the inclusion and exclusion criteria used to identify subjects or sampled population could differ, or study could be conducted with difference study design.

Some of the variables that have been included in other studies for the association of methamphetamine induce psychosis but not in this study were the form of methamphetamine (Dore and Sweeting, 2006), genetic factor (Nakamura *et al.*, 2006), children behaviour-attention deficit hyperactivity disorder (Salo *et al.*, 2008), family history of psychiatric illness (Salo *et al.*, 2008, Chen *et al.*, 2005) and neurotransmitter activity (Yui *et al.*, 2004).

3.6 Conclusions

The prevalence of psychosis among methamphetamine dependent subjects was found to be alarmingly high in this study. Independent risk factors for psychosis were determined; methamphetamine dependent who i) have bipolar mania, ii) have anti-social personality, iii) use higher amount of methamphetamine, or iv) have higher total family income, are at greater risks to develop psychotic symptoms. These findings

3 Methamphetamine Induced-Psychosis

substantiate the fact that methamphetamine users are a high-risk population for psychosis, including those without known history of schizophrenia or other psychotic disorders.

Chapter FOUR: Association of Brain-Derived Neurotrophic Factor (Val66Met) Genetic Polymorphism with Male Methamphetamine Dependence in Malaysia

4.1 Abstract

Introduction: Brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, is widely expressed in the adult mammalian brain and plays an important role in the long-term survival, differentiation, and outgrowth of neurons. Previous studies suggested that the BDNF gene may be involved in the mechanisms underlying substance dependence.

Objectives: This study investigated (i) the association of the BDNF gene Val66Met polymorphism with methamphetamine dependence (ii) the association of the BDNF gene Val66Met polymorphism with the occurrence of psychosis among methamphetamine dependence patients in a Malaysian male population with different ethnicities.

Methodology:

Design : This was a case-control study.

Setting: Cases were recruited from Department of Psychological Medicine, University Malaya Medical Centre (UMMC), Kuala Lumpur, Drug Rehabilitation Centre Papar, Sabah and Prison at Kota Kinabalu, Sabah. Controls were healthy volunteers from University of Malaya Medical Centre (UMMC) and Luyang Health Clinic, Sabah.

Patients: The subjects included all male patients aged more than 18 who fulfilled the Diagnostic and Statistical Manual of

4 BDNF and Methamphetamine Dependence

Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 1994) criteria for methamphetamine dependence.

Cases were defined as male patients with methamphetamine dependence and confirmed by a positive urine test for methamphetamine.

Controls were defined as healthy male subjects who volunteers to participant in this study.

Measures: The Mini International Neuropsychiatric Interview (M.I.N.I.) and a structured questionnaire to assess sociodemographic background. The BDNF Val66Met polymorphism was genotyped by polymerase chain reaction-based methods with forward and reverse primers (PCR-RFLP).

Results: 186 male methamphetamine-dependent subjects and in 154 male controls of four different ethnicities, namely, Malay, Chinese, Kadazan-Dusun, and Bajau were recruited in this study. Our results showed that the distribution of the BDNF Val66Met genotype in Chinese subjects with methamphetamine dependence (OR=2.6, $p=0.015$) and methamphetamine psychosis (OR=0.2, $p=0.034$) were significant compared with controls. The frequency of the 66Val allele in methamphetamine-dependent subjects was higher than that in the control group, suggesting that the 66Val carriers are more susceptible to methamphetamine dependence. However, 66Val allele frequency in

4 BDNF and Methamphetamine Dependence

other ethnicities was not significantly different from the controls. The results of the study also showed that in the Chinese methamphetamine dependent subjects, there was a difference in allele frequency when comparing those who developed psychosis and those who did not.

Conclusion: Our findings suggest that the BDNF Val66Met polymorphism may contribute to methamphetamine dependence and psychosis in the Chinese population but not in other Malaysian ethnicities.

Keywords: Brain-derived neurotrophic factor, Methamphetamine dependence, Psychosis, Association study, Single nucleotide polymorphism

4.2 Introduction

Risk Factors for Methamphetamine Dependence

Methamphetamine abuse can lead to drug dependence when taken often enough and in large enough quantities. However, individuals are differentially vulnerable to methamphetamine dependence. The probability of continuing drug use varies from individual to individual, and the difference is very likely due to both biological and psychosocial factors.

Drug dependence or addiction is a developmental disease that begins in childhood and adolescence. Observations in the past suggested that both genetic and environmental conditions play an important role in predisposing individuals to their drug-taking behaviour (George R.U. *et al.*, 2000) from the initiation of drug use, to regular drug use, addiction and relapse.

Note that not all individuals at risk of drug abuse will start using drugs or become addicted (George R.U. *et al.*, 2000). Furthermore, a risk factor for one person may not be for another. Similarly, the absence of risk factors provides no assurance that a person will not become a drug user.

Genetic Factors

Over the past decades, familial and population genetic studies (Mirin *et al.*, 1991, Rounsaville *et al.*, 1991, Luthar and Rounsaville, 1993) have revealed possible genetic bases for some of the inter-individual

4 BDNF and Methamphetamine Dependence

differences in vulnerability to substance abuse and addiction risk. Twin (Pickens *et al.*, 1995, Johnson *et al.*, 1996, Miles *et al.*, 2001) and adoption (Cadoret *et al.*, 1986, Cadoret *et al.*, 1996) studies have also determined that both genetic and environmental influences are involved in drug use or dependence. Genetic factors and combined genetic-environmental interactions have been estimated to account for 40% to 60% of the variability in addiction risk (Kendler *et al.*, 1994, Tsuang *et al.*, 1998, Kendler *et al.*, 2000).

How Gene Contribute To Dependence Vulnerability

The susceptible single nucleotide polymorphisms in some genes may contribute to addiction vulnerability in several ways, including changing the structure or function of specific proteins. A mutant protein causes structural or functional changes of specific brain circuits during development phase or in adulthood (Nestler, 2000). These altered brain circuits may change an individual's responsiveness to initial drug exposure, or alter the adaptations that occur in the brain after repeated drug exposure.

In addition, allelic variants of specific genes could also (George R.U. *et al.*, 2000):

- Mediate differential drug reinforcing properties.
- Alter drug pharmacodynamics or pharmacokinetics.
- Influence "sensation-seeking" personality attributes that may facilitate exposure to drugs.

4 BDNF and Methamphetamine Dependence

- Exacerbate Drug Toxicities.

Genes in Methamphetamine Dependence Risk

The heritability for psychostimulants has been estimated to be around 66% (Tsuang *et al.*, 1998, Kendler *et al.*, 2000, Tsuang *et al.*, 1996). Genes important in the mesolimbic/mesocortical dopaminergic pathways are known to be strong candidate genes contributing to inter-individual differences in substance abuse vulnerability (George R.U. *et al.*, 2000).

Many of the genetic studies in methamphetamine addiction risk have concentrated on the contribution of genes encoding proteins of the dopamine system, such as the dopamine receptor genes (e.g. DRD1, DRD2), dopamine transporter gene (DAT1), and dopamine beta-hydroxylase gene (DBH) (Rutter, 2006) Dopamine is thought to be essential to the brain's response to drugs like opiates and psychostimulants.

For example, Chen and colleagues(Chen *et al.*, 2004a) examined the DRD2, DRD3 and DRD4 gene variants in 851 methamphetamine subjects with and without psychosis (416 methamphetamine abusers and 435 controls). They found that the 7-repeat (exon III) DRD4 polymorphism occurred more frequently in the methamphetamine abusers than in controls (2% vs 0.6%).

In a follow-up study conducted by Li et al (Li *et al.*, 2004), a modest interaction among the high-activity allele of catechol-O-methyltransferase (COMT) and DRD4 genotypes was noted among the

4 BDNF and Methamphetamine Dependence

methamphetamine abusers. COMT is an enzyme involved in the metabolism of dopamine, adrenalin and noradrenalin. Their observations further demonstrated that genetic variations in the dopamine system may exert an additive effect on the risk of becoming a methamphetamine abuser.

Other candidate genes that may be related to drug addiction to methamphetamine include genes that are pharmacokinetically related to the drug, such as cytochrome P450 (CYP) gene family (Yamada *et al.*, 2005, Sellers and Tyndale, 2000), trace amine receptor 4 (TRAR4) gene (Parker and Cubeddu, 1986, Borowsky *et al.*, 2001, Baud *et al.*, 1985), fatty acid amide hydrolase (FAAH) gene, (Sipe *et al.*, 2002, Flanagan *et al.*, 2006) serotonin transporter gene (Murphy *et al.*, 2004), and superoxide dismutase 2 (SOD2) (Nakamura *et al.*, 2006).

BDNF

Brain-derived neurotrophic factor (BDNF), a member of the nerve growth factor-related family of neurotrophins, is widely expressed in the adult mammalian brain. Evidence indicates that BDNF may be involved in the mechanisms underlying substance abuse (Hofer *et al.*, 1990). BDNF plays an important role in the neurodevelopment of dopaminergic (DA)-related systems. This protein interacts with the meso-limbic DA systems that are involved in the therapeutic response to substance abuse, and it subsequently promotes and maintains dopamine D3 receptor (DRD3) expression (Krebs *et al.*, 2000). Methamphetamine is a drug that easily induces drug conditioning and

4 BDNF and Methamphetamine Dependence

elevated BDNF mRNA. BDNF expression has been found to increase acutely after drug abuse, leading to subsequent long-lasting elevation of DRD3 in the nucleus accumbens, which may facilitate response to drug-associated stimuli and finally induce addictive disorders (Le Foll *et al.*, 2005).

Recent studies have demonstrated that the BDNF gene is associated with vulnerability to drug abuse (Itoh *et al.*, 2005). Furthermore, Flanagin *et al.* (Flanagin *et al.*, 2006) reported that BDNF has been implicated in the behavioural response to psychomotor stimulants and that it potentiates neurotransmitters, which are strongly linked to addiction. They suggested that this gene is a logical candidate gene for the study of addiction. Data derived from animal studies have demonstrated that BDNF modulates dopaminergic and serotonergic functions that are strongly linked to substance abuse (Dluzen *et al.*, 1999). BDNF, located on chromosome 11p13, contains a common and functional single nucleotide polymorphism, rs6265 (Val66Met), at codon 66. This G196A polymorphism results in a valine (Val) to methionine (Met) substitution in the prodomain, which affects intracellular trafficking and activity- dependent secretion of BDNF (Li *et al.*, 2005). A previous study reported that the valine (196G) allele is more commonly methamphetamine dependent and suggested that the GG genotype is a risk factor for substance abuse, related to late onset of substance abuse (Cheng *et al.*, 2005). According to Haile *et al.* (Haile *et al.*, 2009), this BDNF polymorphism is not only linked to methamphetamine dependence, but also to the development of

4 BDNF and Methamphetamine Dependence

methamphetamine psychosis. A study on the human BDNF gene has demonstrated that the Val66Met BDNF gene polymorphism is associated with methamphetamine dependence in methamphetamine-dependent Taiwanese subjects, suggesting that homozygous carriers of the 196G allele are more susceptible to methamphetamine abuse (Cheng *et al.*, 2005). This finding suggested that the Val66Met BDNF polymorphism may confer risk for substance abuse.

4 BDNF and Methamphetamine Dependence

4.2.1. RESEARCH QUESTION

- i). Is Val66Met brain-derived neurotrophic factor (BDNF) polymorphism associated with risk of methamphetamine dependence in male patients?
- ii). Is Val66Met BDNF polymorphism associated with the occurrence of psychosis among methamphetamine-dependent male patients?

4.2.2. STUDY OBJECTIVES

- **General Objective**

To determine whether genetic polymorphism is a risk factor for methamphetamine dependence in male patients.

- **Specific Objectives**

- i). To determine the association between Val66Met BDNF polymorphism and methamphetamine dependence in male patients of different ethnicities.
- ii). To determine the association between Val66Met BDNF polymorphism and the occurrence of psychosis among different ethnicities of methamphetamine-dependent male patients.

4.2.3. HYPOTHESIS

- i). There is an association between Val66Met BDNF polymorphism and methamphetamine dependence male patients in different ethnicity.

4 BDNF and Methamphetamine Dependence

- ii). There is an association between Val66Met BDNF polymorphism and the occurrence of psychosis among different ethnicity of methamphetamine dependence male patients.

4.3 Methodology

4.3.1. Study design

This study was a case-control study.

4.3.2. Study Period

The study period was from June 2007 until June 2011. Data was collected from June 2008 until June 2009.

4.3.3. Location of Study

Cases

- i). Inpatient and outpatient of Department of Psychological Medicine at University Malaya Medical Centre (UMMC)
- ii). Drug Rehabilitation Centre in Papar, Sabah that specializes in the treatment methamphetamine-dependent patients.
- iii). Prison in Kota Kinabalu, Sabah

Controls

- i). Healthy volunteers at University of Malaya Medical Centre
- ii). Healthy volunteers at Luyang Health Clinic, Sabah

4.3.4. Study population

4 BDNF and Methamphetamine Dependence

The subjects included all male patients aged more than 18 who fulfilled the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 1994) criteria for methamphetamine dependence.

i). Definition of Cases and Controls for Methamphetamine dependence

Cases: Cases were defined as male patients with methamphetamine dependence and was confirmed by a positive urine test for methamphetamine during recruitment.

Controls: Controls were defined as healthy male subjects who volunteered to participant in this study. They were medically healthy with no history of chronic medical or surgical illness, had no previous history of psychiatric illness, and did not fulfil the DSM-IV criteria for amphetamine and methamphetamine dependence.

ii). Definition of Cases and Controls for the Occurrence of Psychosis among Methamphetamine Dependence Patients

Cases: Cases were identified by qualified psychiatrists that confirmed the presence of psychosis. The male subjects were considered to have psychosis if they have persecutory delusions and delusions of reference or present with auditory, visual hallucinations or tactile hallucinations.

Controls: Controls were defined as healthy male subjects who volunteers to participant in this study. They had no previous history of

4 BDNF and Methamphetamine Dependence

psychiatric illness and were not dependence for amphetamine and methamphetamine.

4.3.5. Exclusion Criteria

Patients who had the following characteristics were excluded from this study:

- i). Patients with mixed or unclear ethnicity.
- ii). Patients with past history of psychiatric illness.
- iii). Patients with other substance dependence and abuse.

4.3.6. Sample Size

The sample size was calculated using an online programme, namely Power of Association With Errors (PAWE)(Gordon *et al.*, 2002, Gordon *et al.*, 2003) for genetic case-control association studies. Universal sampling was used for the recruitment of the study subjects.

- i). Error Model: Gordon Heath Liu Ott
- ii). $\epsilon_1 = 0.05$, $\epsilon_2 = 0.05$
- iii). Generate the genotype frequencies: Genetic model free method
- iv). Genetic model free method assuming Hardy Weinberg Equilibrium

Case 1 allele frequency =0.667 (G)

Control 1 allele frequency =0.433 (G)

- v). The power of the study was taken at 80% level.

4 BDNF and Methamphetamine Dependence

vi). The significance level of the statistic tests done was at 95% Confidence Interval level and α was set at 0.05. The Null hypothesis was rejected when $p < 0.05$.

vii). The ratio of case to control was taken as 1:1.

Total number of samples (Data with Error):

Minimal sample size for allelic test = Cases 44 : Controls 44

Minimal sample size for genotypic test = Cases 56 : Controls 56

4.3.7. Study variables

Dependent variable

- i). Methamphetamine dependence
- ii). The occurrence of psychosis among methamphetamine dependence

Independent variables

Sociodemographic variables

i). Ethnicity

- Malay
- Chinese
- Kadazan-Dusun
- Bajau

ii). Age

iii). Age of onset for methamphetamine dependence

4 BDNF and Methamphetamine Dependence

Brain-Derived	Neurotrophic	Factor	(BDNF)	Val66Met
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Polymorphism

i). Genotype

- G/G
- G/A
- A/A

ii). Allele

- A
- G

4.3.8. Study instrument

The Mini International Neuropsychiatric Interview (M.I.N.I.) is a short structured diagnostic interview for DSM-IV or ICD-10 psychiatric disorders for the Major Axis I psychiatric disorder.(Sheehan *et al.*, 1998b) It has been widely used in international clinical trials and epidemiological studies (Joling *et al.*, 2008, Van't Veer-Tazelaar *et al.*, 2009). The MINI was available in local language (Sheehan *et al.*, 1998a).

4.3.9. Data collection methods

For cases, all male patients with drug dependence were approached during the study period. Patients were briefed on the study and written consent was obtained. Only patients with urine toxicology screened positive for methamphetamine and within 30 days of last use of the

4 BDNF and Methamphetamine Dependence

methamphetamine were included in the study. A face-to-face interview was conducted using a structured questionnaire to obtain sociodemographic data for cases and controls. The cases were assessed for the occurrence of psychosis by a qualified psychiatrist using the Mini International Neuropsychiatric Interview (M.I.N.I.). Three millilitres of blood was collected from each subject by a standard method in an EDTA tube.

4.3.10. DNA Preparation and Analysis

DNA was extracted from leucocytes by using the QIAmp Blood Kit (Qiagen, Germany). For those who were reluctant to provide blood samples, buccal swab tissues were obtained by the QIAmp Mini Kit (Qiagen, Germany). Genotyping of the Val66Met genetic polymorphism of the BDNF gene (G196A; rs6265) was performed by using polymerase chain reaction (PCR)-based methods with forward and reverse primers (forward, 5'-ACTCTGGAGAGCGTGAAT-3'; reverse, 5'-ATACTGTCACACACGCTC-3', respectively). The PCR reaction was performed under the following conditions: 95 °C for 5 min; then 35 denaturing cycles of 30 s each at 95 °C, 30 s of annealing at the appropriate temperature, and 30 s each at 72 °C for extension, and final elongation at 72 °C for 10min. PCR was carried out by using PCR Master Mix (Fermentas International Inc, Canada). Following that, the restriction fragment length polymorphism (RFLP) method was conducted with restriction enzyme NlaIII (New England Biolabs, USA). The PCR product was digested by NlaIII and the mixture was incubated at 37 °C in a dry-block heater overnight. The temperature

4 BDNF and Methamphetamine Dependence

was then increased to 65 °C for 20 min to terminate the activity of the enzyme. After the DNA was digested by restriction enzyme, products were loaded on 2.5% (w/v) agarose gel stained with GelRed (Biotium, USA) and then electrophoresed. The gel was viewed under UV light to observe restriction patterns. The size and distribution of the band was used to determine the genotype of the DNA sample. The PCR products were chosen randomly for validation by DNA sequencing.

4.3.11. Data Management

The data were checked before ending each interview session and before compilation to ensure completeness. Raw data and DNA results were coded and entered into Statistical Package for Social Sciences (SPSS) Version 16.0. The data were summarized by running frequency distributions and simple descriptive statistics (means and standard deviations). Cleaning for double entry and outliers were done before the analysis.

4.3.12. Data analysis

i). Univariate analyses

Only one independent variable was analyzed at a time. It allowed the researcher to describe the characteristics of the study subjects e.g. cases and controls and their distributions. No comparisons were made at this point. For nominal independent variables, they were described in the form of frequencies and percentages. For continuous independent

4 BDNF and Methamphetamine Dependence

variables, they were summarized and described as means, standard deviations and median.

ii). Bivariate analysis

Pearson's Chi-square test and the Fisher's exact test were used to determine the possible association of ethnicity and Val66Met BDNF polymorphism e.g. BDNF 196G/G genotype, the 196G/A heterozygote, and the 196A/A genotype to methamphetamine dependence as first outcome, or to the occurrence of psychosis among methamphetamine dependence as second outcome. Odds ratio and 95% Confidence Interval were used to determine the association of inter-group comparisons of genotype and allele frequency differences. Continuous data (e.g. age) were analyzed using the t-test. An alpha level of significance 0.05 was set for all analyses.

4.3.13. Ethical consideration

Ethical approval was obtained from Medical Ethics Committee of UMMC. Before any interview, patients were informed regarding the nature and purpose of the study and the respondents were given the assurance that all information given will be treated with confidentiality. A written consent was obtained from the patients prior the interviews.

4.4 Results

A total of 186 subjects (n=186) and 154 controls (n=154) comprising Malay, Chinese, Kadazan-Dusun and Bajau ethnicities were recruited in this study. The demographic distribution for the methamphetamine-dependent and control subjects are summarised in Table 4.1. The overall mean age for the male control subjects was 33.0 ± 12.2 years old while the mean age for the male methamphetamine-dependent subjects was 31.0 ± 8.2 years old. The recorded ages for the methamphetamine-dependent and control subjects were the ages when they were recruited. After stratifying the subjects according to the different ethnic groups, only the age was statistically significant difference for the male Malay, Chinese and Kadazan-Dusun between cases and control.

Results from RFLP indicated that three variants exist in the digestion product: homozygous 66Val (GG), heterozygous (GA), and homozygous 66Met (AA) (Fig. 4.1). The presence of 168-bp and 75-bp bands indicated the existence of the A (66Met) allele; the presence of a 243-bp band indicated the existence of the G (66Val) allele; and the presence of 75-bp, 168-bp, and 243-bp bands indicated the existence of the AG (66Met/66Val) heterozygote. The 100-bp ladder was used as a DNA marker. The products of the RFLP were randomly selected to perform direct DNA sequencing for validation. The frequencies of genotypes and alleles for controls and methamphetamine-dependent subjects are shown in Table 4.2 and 4.3. The genotype distribution in

4 BDNF and Methamphetamine Dependence

both controls and methamphetamine-dependent subjects fulfilled the Hardy–Weinberg equilibrium.

For the Malaysian Chinese population, the differences in the genotype frequency ($p=0.016$) and allele frequency ($p=0.015$) between male controls and male methamphetamine-dependent subjects were found to be significant (Table 4.2 and 4.3). The frequency of carrying the G allele in methamphetamine-dependent subjects was significantly higher ($p=0.015$, odds ratio: 2.6, 95% CI 1.26–5.43) than in the controls. Comparison of the 66Val/66Val genotype with 66Val/66Met plus the 66Met/66Met genotype, revealed that the homozygous carriers of 66Val allele has 4.6 times more risk of being dependent on methamphetamine ($p=0.018$, odds ratio: 4.6, 95% CI 1.42–15.14). Furthermore, comparison between 66Val/66Val with 66Met/66Met showed a significantly increased odds ratio ($p=0.021$, odds ratio: 10.0, 95% CI 1.62–60.91) than in the controls (Table 4.4). However, for the overall data (Table 4.5) and the data of other races, no significant difference was observed.

The frequencies of genotypes and alleles for methamphetamine-dependent subjects with and without psychosis are shown in Table 4.6 and 4.7. With regard to the occurrence of methamphetamine psychosis, no significant difference in either genotype frequency ($p=0.850$) or allele frequency ($p=0.889$) was seen when comparing methamphetamine-dependent subjects who experience psychosis with those who do not. However, examination of the data according to the ethnicities revealed that there was a significant difference in allele

4 BDNF and Methamphetamine Dependence

frequency in the Chinese methamphetamine-dependent subjects ($p=0.034$) (Table 4.7). The frequency of carrying the A allele in Chinese methamphetamine-dependent subjects with psychosis was higher than in the methamphetamine-dependent subjects without psychosis. Comparison of the 66Val allele frequency with 66Met allele frequency revealed a significant difference in odds ratio (OR: 0.2, 95% CI 0.07–0.86, $p=0.034$) (Table 4.8). The results showed no significant difference in genotype and allele frequency between methamphetamine-dependent subjects with and without psychosis among the other races studied (Table 4.9).

The effect of the BDNF Val66Met genetic polymorphism on the age of onset of methamphetamine abuse was also analyzed in 187 methamphetamine-dependent subjects. The mean age of onset for the methamphetamine dependent groups was 24.8 ± 9.0 years old for BDNF 66Val/66Val ($n=57$), 23.2 ± 9.4 years old for BDNF 66Val/66Met ($n=99$), and 23.4 ± 5.9 years old for BDNF 66Met/66Met ($n=31$). For the age of onset among the Chinese dependent group, the mean age was 30.3 ± 8.5 years old for BDNF 66Val/66Val ($n=10$), 32.1 ± 11.4 years old for BDNF 66Val/66Met ($n=12$), and 24.0 ± 11.3 years old for BDNF 66Met/66Met ($n=2$). The age of onset of the methamphetamine-dependent subjects neither in overall dependent subjects ($p=0.539$) nor in Chinese ($p=0.593$), Malay ($p=0.822$), Kadazan-Dusun ($p=0.762$) and Bajau ($p=0.371$) dependent subjects was not significant.

4 BDNF and Methamphetamine Dependence

Figure 4.1 Gel photo of 2.5% (w/v) agarose gel electrophoresis for detection of BDNF Val66Met polymorphism

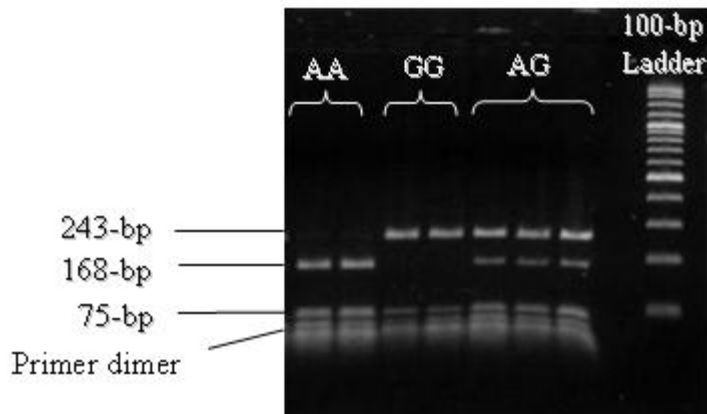


Table 4.1: Demographic data for the male methamphetamine-dependent and the male control subjects

Characteristics	Malay (n = 110)		Chinese (n = 89)		Kadazan-Dusun (n = 80)		Bajau (n = 81)		Total (n = 340)	
	Case (59)	Control (51)	Case (24)	Control (45)	Case (50)	Control (30)	Case (53)	Control (28)	Case (186)	Control (154)
Age (years) mean (SD)	31(7.8)	36(10.6) ++	40(9.6)	30(9.4) ++	29(6.6)	33(11) ++	28(6.4)	31(16.7)	31(8.2)	33(12.2)
Onset age of meth dependence (years), mean (SD)	25(9.1)		31(10.1)		22(7.6)		21(7.1)		24(8.8)	
Meth dependence With psychosis, N (%)	28(47.5)		11(45.8)		14(28.0)		15(28.3)		68(36.6)	
Without psychosis, N (%)	31(52.5)		13(54.2)		36(72.0)		38(71.7)		118(63.4)	

++ t-test: statistical significant

4 BDNF and Methamphetamine Dependence

Table 4.2: Genotype frequencies of the BDNF Val66Met polymorphism in male controls and male methamphetamine-dependent subjects.

Ethnicity	Participant	Genotype n (frequency)			<i>p</i>
		G/G	G/A	A/A	
Malay	Case subject	20(0.34)	33(0.56)	6(0.10)	0.37
	Control	16(0.31)	25(0.49)	10(0.20)	
Chinese	Case subject	10(0.42)	12(0.50)	2(0.08)	0.01*
	Control	6(0.13)	27(0.60)	12(0.27)	
Kadazan-Dusun	Case subject	13(0.26)	28(0.56)	9(0.18)	0.83
	Control	6(0.20)	18(0.60)	6(0.20)	
Bajau	Case subject	13(0.24)	26(0.50)	14(0.26)	0.86
	Control	8(0.29)	14(0.50)	6(0.21)	
Total	Case subject	56(0.30)	99(0.53)	31(0.17)	0.26
	Control	36(0.23)	84(0.55)	34(0.22)	

* statistically significant

4 BDNF and Methamphetamine Dependence

Table 4.3: Allelic frequencies of the BDNF Val66Met polymorphism in male controls and male methamphetamine-dependent subjects

Ethnicity	Participant	Allele frequency			
		G	A	<i>p</i>	OR (CI 95%)
Malay	Case subject	0.62	0.38	0.45	1.3 (0.75-2.20)
	Control	0.56	0.44		
Chinese	Case subject	0.67	0.33	0.01*	2.6(1.26-5.43)*
	Control	0.43	0.57		
Kadazan-Dusun	Case subject	0.54	0.46	0.74	1.2(0.62-2.23)
	Control	0.50	0.50		
Bajau	Case subject	0.49	0.51	0.70	0.8(0.44-1.60)
	Control	0.54	0.46		
Total	Case subject	0.57	0.43	0.13	1.3(0.94-1.73)
	Control	0.51	0.49		

* statistically significant

4 BDNF and Methamphetamine Dependence

Table 4.4: The odds ratio with comparison between allele and genotype frequencies of the *BDNF* Val66Met polymorphism in Chinese controls and Chinese methamphetamine-dependent subjects.

Genotype	<i>p</i>	Odds ratio	95% confidence interval
G vs A	0.01 *	2.6	1.26 – 5.43
GG vs AA	0.02 *	10.0	1.60 – 60.90
GG vs (GA + AA)	0.01 *	4.6	1.42 – 15.14
(GG + GA) vs AA	0.07	3.9	0.88 – 28.11

* Statistically Significant

Table 4.5: The odds ratio with comparison between allele and genotype frequencies of the *BDNF* Val66Met polymorphism in controls and methamphetamine-dependent subjects.

Genotype	<i>p</i>	Odds ratio	95% confidence interval
G vs A	0.11	1.2	0.94 – 1.73
GG vs AA	0.10	1.7	0.89 – 3.25
GG vs (GA + AA)	0.16	1.4	0.86 – 2.31
(GG + GA) vs AA	0.21	1.4	0.82 – 2.44

4 BDNF and Methamphetamine Dependence

Table 4.6: Genotype frequencies of the BDNF Val66Met polymorphism in male methamphetamine-dependent subjects with and without psychosis.

Ethnicity	Participant	Genotype			<i>p</i>
		G/G	G/A	A/A	
Malay	Psychosis	10(0.36)	15(0.54)	3(0.10)	0.94
	No psychosis	10(0.32)	18(0.58)	3(0.10)	
Chinese	Psychosis	2(0.18)	7(0.64)	2(0.18)	0.055
	No psychosis	8(0.62)	5(0.38)	0(0.00)	
Kadazan-Dusun	Psychosis	3(0.21)	8(0.57)	3(0.21)	0.87
	No psychosis	10(0.28)	20(0.55)	6(0.17)	
Bajau	Psychosis	4(0.27)	8(0.53)	3(0.20)	0.80
	No psychosis	9(0.24)	18(0.47)	11(0.29)	
Total	Psychosis	19(0.28)	38(0.56)	11(0.16)	0.85
	No psychosis	37(0.31)	61(0.52)	20(0.17)	

4 BDNF and Methamphetamine Dependence

Table 4.7: Allelic frequencies of the BDNF Val66Met polymorphism in male methamphetamine-dependent subjects with and without psychosis.

Ethnicity	Participant	Allele frequency			
		G	A	<i>p</i>	OR (CI 95%)
Malay	Psychosis	0.63	0.37	0.96	1.1 (0.50-2.22)
	No psychosis	0.61	0.39		
Chinese	Psychosis	0.50	0.50	0.03#*	0.2(0.07-0.86)
	No psychosis	0.81	0.19		
Kadazan-Dusun	Psychosis	0.50	0.50	0.66#	0.8(0.33-1.92)
	No psychosis	0.56	0.44		
Bajau	Psychosis	0.53	0.47	0.73	1.3(0.54-2.96)
	No psychosis	0.47	0.53		
Total	Psychosis	0.56	0.44	0.89	0.9(0.62-1.45)
	No psychosis	0.57	0.43		

Fisher's exact test

*statistically significant

4 BDNF and Methamphetamine Dependence

Table 4.8: The odds ratio with comparison between allele and genotype frequencies of the *BDNF* Val66Met polymorphism in methamphetamine-dependent subjects with psychosis and methamphetamine-dependent subjects without psychosis.

Genotype	<i>p</i>	Odds ratio	95% confidence interval
G vs A	0.89	0.9	0.62 – 1.45
GG vs AA	0.88	0.9	0.37 – 2.40
GG vs (GA + AA)	0.63	0.8	0.43 – 1.63
(GG + GA) vs AA	0.90	1.1	0.47 – 2.44

Table 4.9: The odds ratio with comparison between allele and genotype frequencies of the *BDNF* Val66Met polymorphism in Chinese methamphetamine-dependent subjects with psychosis and methamphetamine-dependent subjects without psychosis.

Genotype	<i>p</i>	Odds ratio	95% confidence interval
G vs A	0.03 *	0.2	0.07 – 0.86
GG vs AA	0.03 *	0.01	0.0 – 0.85
GG vs (GA + AA)	0.04 *	0.2	0.01 – 0.95
(GG + GA) vs AA	0.12	0.01	0.0 – 1.76

* Statistically Significant

4 BDNF and Methamphetamine Dependence

4.5 Discussion

Studies on single nucleotide polymorphisms and its association with methamphetamine dependence have not been previously carried out in Malaysia. This field of study is still a relatively new and interesting field to explore in Malaysia.

The results of this study did not find an association between BDNFVal66Met genotype or allele frequency and methamphetamine dependence in the overall Malaysian subjects studied. This finding was similar to a recent study among 189 methamphetamine abusers from a Japanese population (79.4% male and 20.6% female), BDNF Val66Met polymorphism was not associated with methamphetamine abuse (Itoh *et al.*, 2005). In our study, although this association was not significant overall, the data for the Chinese subgroup suggested that the BDNF Val66Met polymorphism contributes to methamphetamine dependence vulnerability in this ethnicity. The risk for methamphetamine dependence in the Chinese subgroup with the 66Val 169G allele was 2.6, whereas with the 66Val homozygous 196G, it was 4.6, suggesting that this allele may contribute to methamphetamine dependence in the male Chinese population. Although the results of this study showed that the 66Val allele for the Chinese subpopulation is a risk factor for methamphetamine dependence, the age of onset for methamphetamine abuse from either the overall data or the Chinese dependent subjects within the three genotypes was not significant, inconsistent with the results of Cheng *et al.* (Cheng *et al.*, 2005). They reported a significant difference in the age of onset for

4 BDNF and Methamphetamine Dependence

methamphetamine abuse across the three genotype groups ($p=0.048$), perhaps because of involvement of independent genes with a different penetrance level of different susceptibility loci in the pathogenesis of substance dependence. In this study, the 66Met allele was less common in the Chinese methamphetamine-dependent groups than it was in the control group. However, the 66Val/66Val genotype is more common in methamphetamine-dependent groups, and this finding is also compatible with the observation from previous studies which was in Han Chinese population that the Met allele is the dominant allele of the BDNF Val66Met polymorphism (Cheng *et al.*, 2005, Chen *et al.*, 2004b). Furthermore, the odds ratio of being methamphetamine dependent between 66Val/66Val and 66Val/66Met plus the 66Met/66Met genotype ($OR=4.2$) in this study also revealed that the Met allele is the dominant allele of the BDNF Val66Met polymorphism. This finding may indicate that the Chinese population in Malaysia and the Han Chinese have a common origin. The 66Val allelic frequency in our study for the Malaysian Chinese subgroup was 46.4%, comparable with previous findings that showed that the frequency of this allele in normal African-American, European-American, and Chinese people was 13.6%, 33.6%, and 46.7%, respectively. This result suggests that this allele is dominant in the Chinese and European-American population (Cheng *et al.*, 2005, Liu *et al.*, 2005).

Our overall data and stratified analyses by ethnicity showed that the BDNF Val66Met polymorphism was not associated with methamphetamine psychosis among the methamphetamine abusers,

4 BDNF and Methamphetamine Dependence

suggesting that this polymorphism does not cause susceptibility to psychosis in male Malaysian methamphetamine-dependent subjects. This finding is in line with the study of Itoh et al. (Itoh *et al.*, 2005) that showed that the BDNF gene was not associated with methamphetamine psychosis in a Japanese population. Results of this study however, showed a significant difference in allele frequency between those who developed psychosis and those who do not in the Chinese methamphetamine-dependent subjects. In contrast with the methamphetamine dependence, the risk for methamphetamine psychosis with the 66Val 196G allele was 0.2, while with 66Met 196A allele was 4.2 in Chinese methamphetamine-dependent subjects, whereas the methamphetamine dependence with the 66Val 196G allele was 2.6, suggesting that this 66Val allele is more likely to contribute to methamphetamine dependence in the male Chinese population but not for the methamphetamine psychosis. Moreover, 66Met allele may contribute to methamphetamine psychosis but not to methamphetamine dependence. This may be due to variation in definitions of psychosis that is being used in the present study compared to the ones that are being used in other studies, and it may, in part, be due to the small sample size of the methamphetamine psychosis in the present study. Hall et al. (Hall *et al.*, 2003) in an animal study showed that heterozygous BDNF-knockout mice displayed cocaine-conditioned place preferences and reduced locomotion during habituation after cocaine injections. He reported that, compared with 66Met carriers, 66Val/66Val carriers may have higher

4 BDNF and Methamphetamine Dependence

levels of central BDNF, which increases the euphoric effect following methamphetamine administration and renders them more vulnerable to methamphetamine abuse. Our findings were similar to those of Hall et al. (Hall *et al.*, 2003) in that more case subjects than control subjects had the 66 Val variant. There may be several explanations for the contrasting finding between the present study and that of Cheng et al (Cheng *et al.*, 2005). It is possible that our finding is a false positive which is contributed by the impact of stratification on our results.

However, this is not very likely because we do have a relatively homogenous group, especially in gender and the type of drug used, all our subjects being males (Table 4.3) who were on methamphetamine only.

Limitation and Errors

i). Adequacy of sample size

The required minimal sample size for allelic test was 44 cases and 44 controls, whereas minimal sample size for genotypic test was 56 cases and 56 controls. The calculated study sample was based on 80% power of the study for the stratification of ethnic. For this study, only Malay has maintained the power of study for allelic and genotypic test. As for Kadazan-Dusun and Bajau the study subjects was relatively small size, the number of control was 50% lesser than cases, and therefore the potential association cannot be determined.

ii). Comparing findings with other studies

4 BDNF and Methamphetamine Dependence

Other studies might not find the similar findings, either the studies have very different ethnic backgrounds or the sample size was small.

4.6 Conclusions

In conclusion, our results showed a significant difference in the allelic and genotype frequencies in the Malaysian Chinese population for both methamphetamine dependence and psychosis. Our findings suggest that the 66Val/66Val genotype of the BDNF Val66Met polymorphism is a risk factor for methamphetamine dependence. Besides that, the BDNF 66Met allele may contribute to a vulnerability to methamphetamine psychosis in the Chinese population. However our study failed to show any association between BDNF Val66Met polymorphism with occurrence of methamphetamine dependence, and with risk of psychosis in the other ethnic populations and total Malaysian population studied. Further study with a larger sample size may provide more evidence to confirm the genetic influence of BDNF in methamphetamine dependence.

Chapter FIVE: Efficacy and Safety of Aripiprazole in the Treatment of Methamphetamine-Induced Psychosis: An Open Label Prospective Study

5.1 Abstract

Introduction: Methamphetamine-induced psychosis is one of the most widely known side effects associated with high-dose or chronic methamphetamine use. It has been reported that methamphetamine dependent users were three times more likely to experience psychotic symptoms than non-regular methamphetamine users. There is a great need for the treatment of methamphetamine-induced psychosis.

Objectives: The objective of this study was to explore the therapeutic effects and tolerability of aripiprazole in the occurrence of psychosis among methamphetamine-dependent patients.

Methodology:

- Design:* This was an open label single arm prospective study.
- Setting:* Patients were recruited from the inpatient psychiatric wards and outpatient psychiatric clinic in University Malaya Medical Centre(UMMC), Kuala Lumpur.
- Patients:* The study population included male or female with a current Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnosis of methamphetamine dependence. The patients must be having acute

5 Aripiprazole and Methamphetamine-Induced Psychosis

psychotic symptoms due to methamphetamine and the Clinical Global Impression severity (CGI-S) score must be ≥ 4 . Patient must be treatment naive and was not on any psychotropics.

Intervention: Eligible patients were treated with the initial dose of 5-10 mg aripiprazole. From day 2 to day 14, aripiprazole was flexible dosed (5-15mg/day) at the discretion of the treating psychiatrist.

Measures: The primary outcome measure was the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression scale- Severity of Illness (CGI-S). Other scales included the Amphetamine Withdrawal Questionnaire scale (AWQ), Brief Substance Craving Scale (BSCS), Barnes Akathisia Scale (BAS), Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS) and Hospital Anxiety Depression Scale (HADS). Mixed-effects model repeated-measures analysis was utilized to examine changes in outcome measures over time with the treatment aripiprazole.

RESULTS: A total of 49 patients were enrolled and started on aripiprazole. In all, 41 patients (83.7%) completed the study. At baseline the mean PANSS total score was 79.2 ± 13.7 and the mean CGI-S score was 4.3 ± 0.5 . There was a statistically significant decline in the mean PANSS-total and CGI-S score over the course of the

5 Aripiprazole and Methamphetamine-Induced Psychosis

study. The mean reduction was 27.6 ± 21.4 point ($p < 0.05$, 95% CI [-34.8, -20.4] from baseline at day 14 for total PANSS score and 2.0 ± 1.2 point ($p < 0.05$, 95% CI [-2.4, -1.6) for CGI-S. At day 14 the mean PANSS total score was 51.6 ± 14.7 and the mean CGI-S score was 2.3 ± 1.0 . Aripiprazole was generally well tolerated during the study. Adverse events were reported in 10 (20.4%) patients. The reported adverse events were akathisia, insomnia, agitation, sedation and depression. 2 (4.1%) patients discontinued from the study due to akathisia. Most adverse events were mild to moderate in intensity. There was no serious adverse event during the study period. No statistically significant changes were noted with respect to BARS, SAS and AIMS.

CONCLUSIONS: This 2-week, open-label study shows that aripiprazole given once-daily improved the psychotic symptoms associated with methamphetamine dependence. The treatment was generally well tolerated with mild to moderate adverse events. In this study aripiprazole was an efficacious and safe option for the treatment of methamphetamine induce psychosis.

Keywords: Methamphetamine dependence, Methamphetamine induce psychosis, Aripiprazole, Open label study, Safety, Efficacy, Psychosis

5.2 Introduction

Methamphetamine can trigger psychotic symptoms in individuals with no past history of psychosis (Leduc and Mittleman, 1995). Culminating evidence has indicated that chronic use of methamphetamine gradually leads to the development of a psychotic state resembling paranoid schizophrenia (Sato, 1992, Iwanami *et al.*, 1994). It has been reported that methamphetamine dependent users were three times more likely to experience psychotic symptoms than non-regular methamphetamine users (Mcketin *et al.*, 2006b).

Duration of methamphetamine induced psychosis

Although methamphetamine induced psychiatric disorders are typically self-limited and usually abate on their own, treatment is still needed in cases of emergency situations (i.e. acute episodes of methamphetamine induced psychosis), as well as to prevent recurrence in long-term. Recurrence of psychotic symptoms can occur due to continued use of methamphetamine or other drug use and also due to psychosocial stressors (Yui *et al.*, 1997, Yui *et al.*, 2000).

In some cases psychosis may persist and around 5 -15% of users who developed methamphetamine psychosis fails to recover completely (Hofmann, 1983). When the psychotic symptoms persist and interfere with the patient's social and occupational functioning, treatment should be targeted to psychiatric symptoms present (Larson, 2008).

Medical management of methamphetamine psychosis

Psychotic symptoms occur most often during intoxication; therefore, treatment of methamphetamine psychosis should focus on controlling medical and psychiatric symptoms while eliminating the offending substance (Larson, 2008).

Medical therapy of methamphetamine induced psychosis involves stabilizing and minimizing the symptoms of psychosis (e.g. agitation). Firstly, methamphetamine need to be removed from the body (Larson, 2008). To achieve this, charcoal, for example, can be used to eliminate methamphetamine from the gastrointestinal and circulatory systems.

In emergency situation, clinicians normally select a high-potency antipsychotic (e.g. haloperidol) for administration, as antipsychotics help control psychotic symptoms and provide rapid tranquilization of the agitated patients (Larson, 2008). Table 5.1 below lists other types of treatment that can be rendered during an acute episode of methamphetamine-induced psychosis.

5 Aripiprazole and Methamphetamine-Induced Psychosis

Table 5.1: Treatment of acute methamphetamine induced psychosis

Benzodiazepines (Lorazepam, Chlordiazepoxide)	<ul style="list-style-type: none">• Primarily used to sedate agitated patients• Available in oral, intravenous injection and intramuscular injection forms, allowing the drug to be used in emergency situations
Opiate antagonists (Naloxone)	<ul style="list-style-type: none">• Inhibit the action of opiates
Beta-blockers (Propanolol)	<ul style="list-style-type: none">• Useful in patients who are agitated, anxious, and hyper-arousable due to methamphetamine use• Temporarily used until methamphetamine is eliminated from the patient's body system• In prolonged anxiety, non-addictive beta-blockers may be helpful
Expectorants (Ammonium chloride)	<ul style="list-style-type: none">• Mainly used to acidify the urine and increase methamphetamine excretion when intoxication from methamphetamines resulted in psychiatric and medical complications• Available in PO form; patient must be able to swallow or receive a nasogastric tube
Adsorbents(Activated charcoal suspension)	<ul style="list-style-type: none">• Given through a nasogastric tube into the stomach• Absorb intentionally and accidentally ingested substances to prevent further absorption into the systemic circulation

(Larson, 2008)

Clinical evidence on treatment of methamphetamine psychosis

To date, there is little empirical evidence on which to base treatment approaches to methamphetamine induced psychosis. Most published

5 Aripiprazole and Methamphetamine-Induced Psychosis

treatment consists of case reports and small open label studies (Srisurapanont *et al.*, 2001b). There is currently no approved medication by the Food and Drug Administration (FDA) or the Malaysian Drug Authority to be used in the treatment of methamphetamine induce psychosis.

Two early studies showed that agitation and some psychotic symptoms may subside within an hour after an antipsychotic injection in methamphetamine users. The first study (Angrist *et al.*, 1974) showed that haloperidol intramuscular administration significantly reduced the symptoms of excitement and paranoid ideation within an hour. The second study (Richards *et al.*, 1998) demonstrated that droperidol (a butyrophenon) could sedate agitated methamphetamine users significantly faster than lorazepam after intravenous administration.

Other than that, case studies of methamphetamine psychosis have reported good responses to olanzapine (Misra *et al.*, 2000), risperidone (Misra and Kofoed, 1997) and quetiapine (Dore and Sweeting, 2006).

Current research evidence available suggests that the most commonly used agents for the acute treatment of methamphetamine-induced psychosis are benzodiazepines and antipsychotics (Mcketin *et al.*, 2006b). In Australia, the most commonly prescribed antipsychotic was olanzapine, while in Thailand and the Philippines it was haloperidol (Mcketin *et al.*, 2006a).

Aripiprazole in the treatment of methamphetamine induced psychosis

Aripiprazole, the sixth atypical antipsychotic medication, was first approved by the Food and Drug Administration (FDA) in 2002 for the treatment of schizophrenia. Available as tablets for oral administration, aripiprazole is also indicated for the treatment of acute manic episodes associated with bipolar 1 disorder since 2004.

Pharmacology of aripiprazole

Unlike other atypical antipsychotics (e.g. olanzapine, quetiapine, risperidone) that act as antagonist at D₂ dopamine receptors (Kapur, 2004, Strange, 2001), aripiprazole appears to mediate its antipsychotic effects primarily by partial agonism at D₂ receptors (Burris *et al.*, 2002, Grunder *et al.*, 2003, Yokoi *et al.*, 2002), which are responsible for dopaminergic activity modulation.

A partial agonist has a lower intrinsic activity at the receptors than a full agonist (i.e. the naturally occurring neurotransmitters), allowing it to act either as a functional agonist or a functional antagonist, depending on the surrounding levels of the intrinsic full agonist (Lieberman, 2004).

In the absence of a full agonist, a partial agonist shows functional agonist activity – binding to the receptor to produce a response. In the presence of a full agonist, on the other hand, a partial agonist shows

5 Aripiprazole and Methamphetamine-Induced Psychosis

functional antagonist activity – receptor binding reduces the response generated by the full agonist.

This partial agonist effect stabilizes dopamine receptors while allowing a modulation of function, rather than blocking them exclusively (Stahl, 2001). Therefore, partial agonists are also known as dopamine system stabilizers, which constitute a new class of antipsychotic agents without leading to apparent motor side effects (Stahl, 2001).

It is the partial dopamine agonist effect of this drug that aripiprazole has been tested for its effects in reducing cocaine cravings in schizophrenic cocaine-dependent subjects (Beresford *et al.*, 2005). It was hypothesized that aripiprazole acts either through lowering dopamine over-activity or through increasing dopamine under-activity, or through some combination of both.

In addition, aripiprazole also functions as a partial agonist at the serotonin 5-HT_{1A} receptors and, like the other atypical antipsychotics, displays an antagonist profile at the serotonin 5-HT_{2A} receptors (Torrent, 2003). Aripiprazole has moderate affinity for histamine H₁ receptors and alpha₁-adrenergic receptors, and no appreciable affinity for cholinergic muscarinic receptors (Torrent, 2003). Actions at receptors other than D₂, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole. For instance, the orthostatic hypotension observed with aripiprazole may be attributed to its antagonist activity at adrenergic alpha₁ receptors (Torrent, 2003).

Clinical pharmacokinetics of aripiprazole(Torrent, 2003)

Aripiprazole activity is most likely due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which is also known to have affinities for D₂ receptors. Dehydro-aripiprazole represents 40% of its parent drug exposure in plasma.

Steady-state plasma concentrations are achieved within 14 days of dosing for both aripiprazole and dehydro-aripiprazole. Both parent drug and active metabolite have elimination half-lives of 75 hours and 95 hours, respectively. At steady state, the pharmacokinetics of aripiprazole is dose-proportional.

Aripiprazole is well absorbed. Its maximum plasma concentration (C_{Max}) is achieved within 3-5 hours after oral dosing, with an absolute oral bioavailability of 87%. Absorption of this drug is not affected by food.

Aripiprazole undergoes extensive hepatic metabolism involving the cytochrome P450 isozymes CYP3A4 and CYP2D6. Aripiprazole is usually excreted in trace amount (<1%) in the urine, while about 18% of the oral dose is recovered unchanged in the feces.

Co-administration of aripiprazole with medications that may inhibit (e.g. paroxetine, fluoxetine) or induce (e.g. carbamazepine) the metabolic enzymes may lead to an increase or a decrease of plasma concentrations of aripiprazole, respectively.

Aripiprazole in the treatment of psychiatric disorders

The effects of aripiprazole in psychiatric disorders have been mainly investigated in schizophrenia. In schizophrenia, excessive dopamine activity is thought to cause positive symptoms, while reduced dopamine activity leads to negative symptoms and cognitive impairment. A partial agonist will act as a functional antagonist in the mesolimbic dopamine pathway where dopamine activity is excessive, but show functional agonist activity in the mesocortical pathway where dopamine activity is low (Lieberman, 2004).

In addition, a partial agonist is likely to avoid complete blockade of the nigrostriatal or tuberoinfundibular pathways, which are associated with extra-pyramidal symptoms (EPS) and elevated prolactin levels, respectively (Lieberman, 2004).

Clinical trials with aripiprazole have demonstrated the value of partial agonist treatment approach. Aripiprazole has been shown to produce significant improvements in positive and negative symptoms in short- and long-term studies of patients with schizophrenia or schizoaffective disorder (Lieberman, 2004).

In both short- and long-term studies, aripiprazole treatment was well tolerated, showing a low liability for EPS and hyperprolactinemia, a lack of QTc prolongation, and minimal weight gain or sedation (Lieberman, 2004).

5 Aripiprazole and Methamphetamine-Induced Psychosis

More recently, aripiprazole was shown to be useful in treating psychosis associated with Parkinson's Disease (Keck *et al.*, 2007) and preventing relapse in bipolar 1 disorder (Lopez-Meza *et al.*, 2005), as well as an effective and safe adjunctive therapy to standard antidepressant treatment in patients with major depressive disorder (Marcus *et al.*, 2008).

The proven efficacy of aripiprazole in a number of psychiatric disorders thus provides a rationale for investigating this drug in the treatment of methamphetamine induced psychosis.

Tolerability and safety of aripiprazole (Torrent, 2003)

The most common adverse events associated with aripiprazole therapy include:

- Insomnia, restlessness;
- Headache, dizziness, akathisia, somnolence or sedation, tremor;
- Blurred vision;
- Tachycardia;
- Orthostatic hypotension;
- Nausea, vomiting, constipation, dyspepsia.

Other adverse effects known to be associated with antipsychotic therapy have also been reported during treatment with aripiprazole, including (Torrent, 2003):

5 Aripiprazole and Methamphetamine-Induced Psychosis

- Neuroleptic syndrome;
- Tardive dyskinesia;
- Seizure;
- Cerebrovascular events and increased mortality in elderly demented patients;
- Hyperglycemia and diabetes mellitus.

Rare adverse events associated with aripiprazole are such as allergic reactions and a potentially fatal symptom complex known as neuroleptic malignant syndrome (NMS) (Torrent, 2003). Patients who develop NMS may have, among the symptoms, high fevers, muscle rigidity, rapid heart rate, excessive sweating and heart arrhythmias.

Nevertheless, when compared with other typical antipsychotics for treating schizophrenia and schizophrenia-like psychoses, the latest Cochrane review (Bhattacharjee and El-Sayeh, 2008) revealed that aripiprazole, despite producing similar efficacy as typical antipsychotic drugs, presents significant advantages in terms of tolerability.

There were fewer occurrences of extra-pyramidal symptom, and particularly akathisia, fewer incidences of hyperprolactinemia and raised fasting blood glucose, and lesser risk of sinus tachycardia and blurred vision in patients treated with aripiprazole compared with those who received typical antipsychotic therapy (Bhattacharjee and El-Sayeh, 2008).

5 Aripiprazole and Methamphetamine-Induced Psychosis

This favorable adverse effects profile of aripiprazole may help enhance its effectiveness in treatment compliance.

While evidence clearly suggests aripiprazole to be a well-tolerated treatment in patients with psychiatric disorders, there is still little known about its tolerability in methamphetamine dependent subjects. Therefore, studies of the safety and efficacy of aripiprazole in this group of individuals are urgently warranted to determine its role in the treatment methamphetamine induced psychosis.

5.3 Systematic review on the efficacy and safety of aripiprazole in the treatment of methamphetamine-induced psychosis.

5.3.1. Methods

5.3.2. Search strategy

This systematic review included literature published between January 2000 and March 2011. An electronic search on the following databases was carried out: PUBMED, Web of Science, OVID Medline (R), the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Review, using the search terms:

Systematic review 1

- (a) Methamphetamine or Methamfetamine
- (b) Aripiprazole
- (c) Drug-induced psychosis or psychoses

Systematic review 2

- (a) Amphetamine
- (b) Aripiprazole
- (c) Drug-induced psychosis or psychoses

Where Medical Subject Headings (MeSH) terms were available, they were exploded and combined. Reference lists from retrieved papers were also searched.

5.3.3. Type of studies

Only publication in English for experimental studies (e.g. randomized clinical trials and quasi-randomized studies) and systematic review were included if:

- (a) Participants were treated with aripiprazole
- (b) Psychosis or changes in psychosis were measured in a standardised manner.

5.3.4. Types of participant

Male or female patients, of any age or ethnic origin, who has methamphetamine or amphetamine dependence and methamphetamine or amphetamine-induced psychosis.

5.3.5. Types of intervention

The treatment group was aripiprazole.

5.3.6. Types of outcome measures

The changes in psychosis, retention rate of the study, treatment response rate.

5.3.7. Data extraction

Information was extracted on data source such as participants, interventions, results and outcome.

5.3.8. Results

5 Aripiprazole and Methamphetamine-Induced Psychosis

A total of 2 experimental studies for methamphetamine-induced psychosis and 1 experimental study for amphetamine-induced psychosis were identified by the search and cross-referencing strategies.

Figure 5.1 Flow chart showing the article-identification process for methamphetamine-induced psychosis

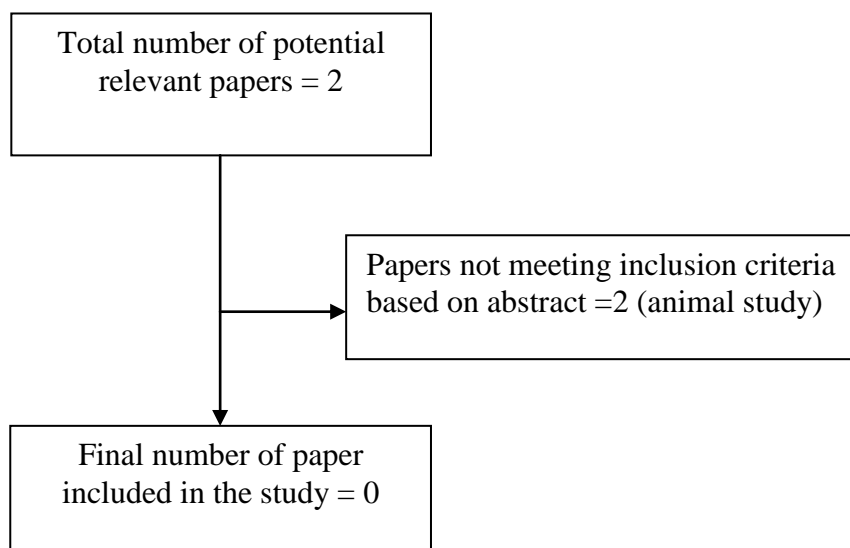
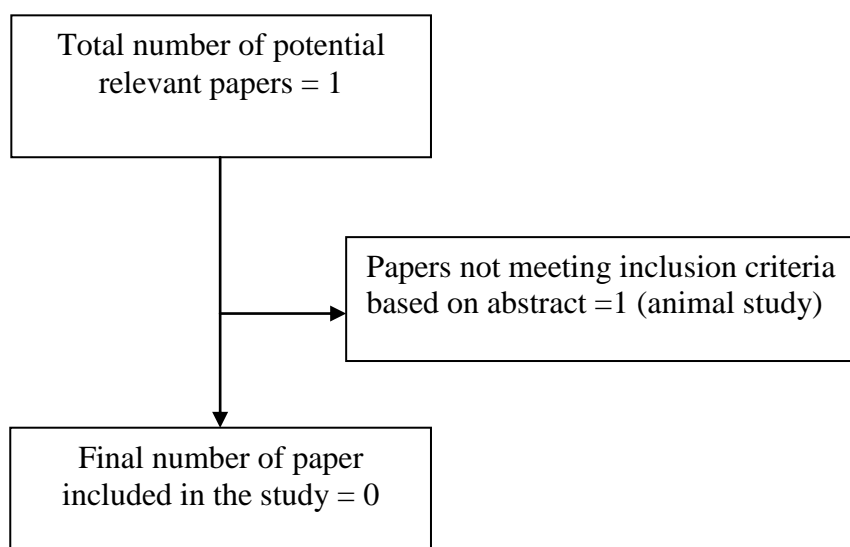


Figure 5.2 Flow chart showing the article-identification process for amphetamine-induced psychosis



5.3.9. RESEARCH QUESTION

What is the efficacy and safety of aripiprazole in the treatment of methamphetamine-induced psychosis patients?

5.3.10. STUDY OBJECTIVES

Primary Objective

To determine the efficacy of aripiprazole in the treatment of methamphetamine-induced psychosis patients.

Secondary objectives

- i). To determine the efficacy of aripiprazole using PANSS subscales in the treatment of methamphetamine-induced psychosis patients.
- ii). To determine the efficacy of aripiprazole in improving the methamphetamine withdrawal and craving symptoms among patients with methamphetamine-induced psychosis.
- iii). To determine the efficacy of aripiprazole in improving the depressive and anxiety symptoms among patients with methamphetamine-induced psychosis.

Tertiary Objective

- i). To determine the safety of aripiprazole in the treatment of methamphetamine-induced psychosis patients.
- ii). To describe the adverse events of aripiprazole in the treatment of methamphetamine-induced psychosis patients.

5.3.11. HYPOTHESES

Hypothesis for primary objective:

- i). Aripiprazole-treated patients will show a significant reduction in the means total Positive and Negative Symptoms Scale (PANSS) score between baseline and day 4.
- ii). Aripiprazole-treated patients will show a significant reduction in the means total Positive and Negative Symptoms Scale (PANSS) score between baseline and day 7.
- iii). Aripiprazole-treated patients will show a significant reduction in the means total Positive and Negative Symptoms Scale (PANSS) score between baseline and day 14.
- iv). Aripiprazole-treated patients will show a significant reduction in the means total Positive and Negative Symptoms Scale (PANSS) score between baseline and day 4, 7 and 14.

Hypothesis for secondary objective:

- i). Aripiprazole-treated patients will show a significant reduction in the means positive symptoms PANSS subscale score between baseline and day 4.
- ii). Aripiprazole-treated patients will show a significant reduction in the means positive symptoms PANSS subscale score between baseline and day 7.

5 Aripiprazole and Methamphetamine-Induced Psychosis

- iii). Aripiprazole-treated patients will show a significant reduction in the means positive symptoms PANSS subscale score between baseline and day 14.
- iv). Aripiprazole-treated patients will show a significant reduction in the means negative symptoms PANSS subscale score between baseline and day 4.
- v). Aripiprazole-treated patients will show a significant reduction in the means negative symptoms PANSS subscale score between baseline and 7.
- vi). Aripiprazole-treated patients will show a significantly reduction in the means negative symptoms PANSS subscale score between baseline and day 14.
- vii). Aripiprazole-treated patients will show a significant reduction in the means general psychopathological PANSS subscale score between baseline and day 4.
- viii). Aripiprazole-treated patients will show a significant reduction in the means general psychopathological PANSS subscale score between baseline and day 7.
- ix). Aripiprazole-treated patients will show a significantly reduction in the means general psychopathological PANSS subscale score between baseline and day 14.

5 Aripiprazole and Methamphetamine-Induced Psychosis

- x). Aripiprazole-treated patients will show a significant reduction in the means Clinical Global Impression – Severity of Illness (CGI-S) scale score between baseline and day 4.
- xi). Aripiprazole-treated patients will show a significant reduction in the means Clinical Global Impression – Severity of Illness (CGI-S) scale score between baseline and day 7.
- xii). Aripiprazole-treated patients will show a significant reduction in the means Clinical Global Impression – Severity of Illness (CGI-S) scale score between baseline and day 14.
- xiii). Aripiprazole-treated patients will show a significant reduction in the means Clinical Global Impression – Severity of Illness (CGI-S) scale score between baseline and day 4, 7 and 14.
- xiv). Aripiprazole-treated subjects will show a significantly greater reduction in Amphetamine Withdrawal Questionnaire (AWQ) means score between baseline and day 4.
- xv). Aripiprazole-treated subjects will show a significantly greater reduction in Amphetamine Withdrawal Questionnaire (AWQ) means score between baseline and day 7.
- xvi). Aripiprazole-treated subjects will show a significantly greater reduction in Amphetamine Withdrawal Questionnaire (AWQ) means score between baseline and day 14.

5 Aripiprazole and Methamphetamine-Induced Psychosis

xvii). Aripiprazole-treated subjects will show a significantly greater reduction in Amphetamine Withdrawal Questionnaire (AWQ) means score between baseline and day 4, 7 and 14.

xviii). Aripiprazole-treated subjects will show a significantly greater reduction in Brief Substance Craving Scale (BSCS) means score between baseline and day 4.

xix). Aripiprazole-treated subjects will show a significantly greater reduction in Brief Substance Craving Scale (BSCS) means score between baseline and day 7.

xx). Aripiprazole-treated subjects will show a significantly greater reduction in Brief Substance Craving Scale (BSCS) means score between baseline and day 14.

xxi). Aripiprazole-treated subjects will show a significantly greater reduction in Brief Substance Craving Scale (BSCS) means score between baseline and day 4, 7 and 14.

xxii). Aripiprazole-treated subjects will show a significantly greater reduction in Hospital Anxiety Depression Scale (HADS) means scores between baseline and day 14.

Hypothesis for tertiary objective:

Aripiprazole-treated patients will not show a significant increase in Barnes Akathisia Scale (BAS), Simpson Angus Scale (SAS) and Abnormal Involuntary Movement Scale (AIMS) scores between baseline and day 4, 7 and 14.

5.4 Methodology

5.4.1. Study Design

This study was an open-label single arm prospective study.

5.4.2. Study Period

The study period was from July 2007 until June 2011. Data was collected from September 2008 to December 2010.

5.4.3. Location of Study

This study was conducted at the inpatient psychiatric wards and outpatient psychiatric clinic in University Malaya Medical Centre (UMMC).

5.4.4. Study Population

The study population included males or females with a current Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnosis of methamphetamine dependence.

5.4.5. Inclusion Criteria

- i). Male or female, aged 18 – 65 years.
- ii). Patient with moderate to severe psychosis with CGI-S \geq 4.
- iii). Severity score of at least 4 on at least one of the Positive and Negative Symptoms Scale (PANSS)-items: P1 – Delusions, P3 - Hallucinatory behaviour, P4 – Excitement, P6 – Suspiciousness/persecution, or G9 – Unusual thought content.

5 Aripiprazole and Methamphetamine-Induced Psychosis

- iv). Duration of psychosis for more than 2 weeks.
- v). Must have been using methamphetamine at least once a week for the past three months at enrollment.
- vi). Urine positive for methamphetamine and within 30 days of last use of the methamphetamine.
- vii). Patient must be treatment naïve, was not on any psychotropics.
- viii). Patient must not have current dependence with other substances such as alcohol, cocaine, opiates and marijuana. However, the past history abusing of these drugs was allowed for this study.
- ix). Present without any current intoxication effects of methamphetamine to provide written informed consent at the time of the baseline session and to comply with study procedures.
- x). Using a barrier (diaphragm or condom) with spermicide, intrauterine device (IUD), or complete abstinence as a method of birth control (if a woman of child-bearing capacity).
- xi). Patient was not suicidal or homicidal.

5.4.6. Exclusion Criteria

- i). Serious medical illnesses that potentially progress to life-threatening medical illness which may compromise patient safety or study conduct.
- ii). Known hypersensitivity or allergy to Aripiprazole.

5 Aripiprazole and Methamphetamine-Induced Psychosis

- iii). Documented history of schizophrenia, bipolar, organic brain disease, dementia, or any diseases that require other antipsychotics.
- iv). Unstable diabetes mellitus
- v). An absolute neutrophil count (ANC) of $\leq 1.5 \times 10^9$ per liter;
- vi). Abnormal ECG.
- vii). Clinically significant abnormal laboratory values.
- viii). Female who is positive on a urine pregnancy test or lactating.

5.4.7. Sample size estimation

Based on previous study (Leucht *et al.*, 2006), the minimum sample size required for this study was calculated by using the PS software.

- i). The power of the study is taken at 80% level for paired *t*-test of PANSS score.
- ii). The significance level of the statistic tests done was at 95% Confidence Interval level and α was set at 0.05. The Null hypothesis was rejected when $p < 0.05$.
- iii). Δ – the difference in the mean of matched pairs is 10 for PANSS score.
- iv). Σ – the standard deviation of difference in the response of matched pairs is 20.

Therefore the sample size obtained for this study as follow:

Total number of subjects = 33 patients

5.4.8. Study Variables

The study variables that were considered for analysis in this study population were as follows:

(Operational definitions and scale in ANNEX A)

5.4.9. Primary Study Endpoints

The efficacy of aripiprazole in the treatment of methamphetamine induce psychosis:

- i). The means scores of total PANSS rating scale

Patients were assessed between baseline and day 4, 7 and 14.

5.4.10. Secondary Study Endpoint

- i). The means scores of positive symptoms PANSS subscale
- ii). The means scores of negative symptoms PANSS subscale
- iii). The means scores of general psychopathological PANSS subscale
- iv). The means scores of CGI-S rating scale
- v). The means scores of Amphetamine Withdrawal Questionnaire (AWQ) scale.
- vi). The means scores of Brief Substance Craving Scale (BSCS) scale.
- vii). The means scores of Hospital Anxiety Depression Scale (HADS) scale.(only day 14)

Patients were assessed between baseline and day 4, 7 and 14.

5.4.11. Tertiary Study Endpoint

The safety of aripiprazole in methamphetamine induce psychosis:

- i). The means scores of BAS rating scale
- ii). The means scores of SAS rating scale
- iii). The means scores of AIMS rating scale
- iv). To describe all adverse events reported by patients during the study.

Patients were assessed between baseline and day 4, 7 and 14.

5.4.12. Descriptive Variables

Sociodemographic and Baseline Characteristics

- i). Age
- ii). Sex
- iii). Race
- iv). Marital status
- v). Educational level
- vi). Employment pattern
- vii). Duration of full time employment
- viii). Total family income
- ix). Methamphetamine use history

- x). History of medical/surgical illness

5.4.13. Study Instruments

i). **MINI International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.*, 1998b)**

This was a face-to-face structured interview for the Major Axis I psychiatric disorder in DSM-IV and ICD-10. The M.I.N.I. is a short structured diagnostic interview for DSM-IV or ICD-10 psychiatric disorders for the Major Axis I psychiatric disorder including suicidality. It has been widely used in international clinical trials and epidemiological studies (Joling *et al.*, 2008, Van't Veer-Tazelaar *et al.*, 2009). The MINI was available in local language (Sheehan *et al.*, 1998a).

ii). **Amphetamine Withdrawal Questionnaire (AWQ) (James *et al.*, 2004)**

A short, reliable and valid questionnaire for the evaluation of amphetamine withdrawal symptom. Items of the AWQ were based on the fourth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) and a comprehensive review. A field trial for assessing the reliability, validity and factor structure was conducted in outpatients and inpatients with amphetamine withdrawal. The AWQ internal consistency was satisfactory with a Cronbach's alpha of 0.77. For test-retest reliability, a Spearman rank order correlation coefficient of the AWQ total score was 0.79. The AWQ total score for criterion

validity was moderately correlated with the other two accepted measures. Principal component analysis, eigenvalue-one test and a varimax rotation performed to elicit the factors of AWQ yielded a three-factor model of AWQ: namely hyperarousal, reversed vegetative and anxiety factors.

iii). Brief Substance Craving Scale (BSCS) (Somoza E, 1999a)

The BSCS uses Likert scales, ranging from 0 to 4, to assess methamphetamine craving on 3 dimensions of craving: intensity, length, and frequency. A composite score is derived from the total of these items.

iv). Positive and Negative Symptoms Scale (PANSS) (Kay *et al.*, 1987)

The Positive and Negative Syndrome Scale(PANSS) is a medical scale used for measuring symptom severity of patients with schizophrenia. It refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association: positive symptoms, which refer to an excess or distortion of normal functions (e.g. hallucinations and delusions), and negative symptoms, which represent a diminution or loss of normal functions. A face-to-face interview of the scale will capture three components: positive scale (7 items), negative scale (7 items) and general psychopathology scale(16 items).

v). **Abnormal Involuntary Movement Scale (AIMS) (Rush, 2000)**

The Abnormal Involuntary Movement Scale (AIMS) is a rating scale that was originally designed in Italian language in the 1980s (Burti *et al.*, 1981), to measure involuntary movements known as tardive dyskinesia (TD). TD is a disorder that sometimes develops as a side effect of long-term treatment with neuroleptic (antipsychotic) medications. The AIMS test is used not only to detect tardive dyskinesia but also to follow the severity of a patient's TD over time. It is a valuable tool for clinicians who are monitoring the effects of long-term treatment with neuroleptic medications and also for researchers studying the effects of these drugs. The AIMS test was originally developed for administration by trained clinicians.

Description

The entire test can be completed in about 10 minutes. The AIMS test has a total of twelve items rating involuntary movements of various areas of the patient's body. These items are rated on a five-point scale of severity from 0–4. The scale is rated from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe). Two of the 12 items refer to dental care. The patient must be calmed and sitting in a firm chair that doesn't have arms, and the patient cannot have anything in his or her mouth. The clinician asked the patient about the condition of his or her teeth and dentures, or if he or she was having any pain or discomfort from dentures.

5 Aripiprazole and Methamphetamine-Induced Psychosis

The remaining 10 items refer to body movements themselves. In this section of the test, the clinician or rater asked the patient about body movements. The rater also looked at the patient in order to note any unusual movements first-hand. The patient was asked if he or she had noticed any unusual movements of the mouth, face, hands or feet. If the patient said yes, the clinician then asked if the movements annoy the patient or interfere with daily activities. Next, the patient was observed for any movements while sitting in the chair with feet flat on the floor, knees separated slightly with the hands on the knees. The patient was asked to open his or her mouth and stick out the tongue twice while the rater watched. The patient was then asked to tap his or her thumb with each finger very rapidly for 10–15 seconds, the right hand first and then the left hand. Again the rater observed the patient's face and legs for any abnormal movements.

After the face and hands had been tested, the patient was then asked to flex (bend) and extend one arm at a time. The patient was then asked to stand up so that the rater can observe the entire body for movements. Next, the patient was asked to extend both arms in front of the body with the palms facing downward. The trunk, legs and mouth were again observed for signs of TD. The patient then walked a few paces, while his or her gait and hands were observed by the rater twice.

A rating of 2 or higher on the AIMS scale, however, is evidence of tardive dyskinesia. If the patient has mild TD in two areas or moderate movements in one area, then he or she should be given a diagnosis of

TD. The AIMS test is considered extremely reliable when it is given by experienced raters.

vi). Barnes Akathisia Scale (BARS) (Barnes, 1989)

The Barnes Akathisia Scale (commonly known as BAS or BARS) is a rating scale that is administered by physicians to assess the severity of drug-induced akathisia. The Barnes Akathisia Scale is the most widely used rating scale for akathisia. This scale includes objective and subjective items such as the level of the patient's restlessness. It comprises items for rating the observable, restless movements which characterise the condition, the subjective awareness of restlessness, and any distress associated with the akathisia. In addition, there is an item for rating global severity. A standard examination procedure is recommended. The inter-rater reliability for the scale items (Cohen's kappa) ranged from 0.738 to 0.955.

Akathisia is a syndrome of motor restlessness, principally seen in association with antipsychotic medication. It is characterized by a subjective experience of mental unease and the urge to move, and manifests physically as particular patterns of restless movement.

vii). Simpson Angus Scale (SAS) (Simpson and Angus, 1970)

Simpson-Angus Scale (SAS) is a 10-item rating scale that has been used widely for assessment of Neuroleptic-Induced Parkinson in both clinical practice and research settings. It consists of one item measuring gait (hypokinesia), six items measuring rigidity and three

items measuring glabella tap, tremor and salivation, respectively. Items are rated for severity on a 0-4 scale, with definitions given for each anchor point. It is an established rating scale. SAS is a reliable and a valid instrument. It performs well and similarly to DSM-IV in Neuroleptic Induce Parkinsonism case detection (Janno *et al.*, 2005).

viii). Clinical Global Impression Scale – Severity of Illness (CGI-S)

The Clinical Global Impression rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders (Guy, 1976). Many researchers, while recognizing the validity of the scale, consider it to be subjective as it requires the user of the scale to compare the subjects to typical patients in the clinician experience (Huber *et al.*, 2008, Haro *et al.*, 2003).

The Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1=normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

ix). Hospital Anxiety Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) was developed by Zigmond and Snaith (Zigmond and Snaith, 1983) in 1983. Its purpose is to provide clinicians with an acceptable, reliable, valid and easy to use practical tool for identifying and quantifying depression and anxiety. The role of the scale is dimensional rather than categorical; it is best used not to make diagnoses of psychiatric disorders, but for identifying general hospital patients who need further psychiatric evaluation and assistance (Herrmann, 1997).

The HADS is a self-report rating scale of 14 items on a 4-point Likert scale (range 0–3). It is designed to measure anxiety and depression (7 items for each subscale). The total score is the sum of the 14 items, and for each subscale the score is the sum of the respective seven items (ranging from 0–21). It is worth noting that items referring to depression symptoms that describe somatic aspects of depression (e.g. insomnia and weight loss) are not included in the scale.

The HADS has been translated and widely used in more than 25 countries since its original development. Herrmann, in an extended review, reported that the HADS has demonstrated reliability and validity when used to assess medical patients (Herrmann, 1997). Bjelland reached similar conclusions in his review 5 years later (Bjelland *et al.*, 2002). The HADS has been used in the general population (Mykletun *et al.*, 2001), on general hospital patients

5 Aripiprazole and Methamphetamine-Induced Psychosis

(Johnston *et al.*, 2000), in cancer care settings (Moorey *et al.*, 1991), and even in HIV patients (Savard *et al.*, 1998).

x). Structured Questionnaires

The patient baseline characteristics were obtained by using a structured questionnaire. The information such as demographic data, history of methamphetamine use, past medical and surgical history were recorded in case record form (CRF).

5.4.14. Study Drug

5.4.14.1 Intervention

Aripiprazole is a psychotropic drug. It is a light yellow colored, round, flat, bevelled edged, uncoated tablets that contain 10mg of aripiprazole.

5.4.14.2 Concomitant Therapy

The concomitant medications such as benzodiazepine and benzhexol were allowed for this study.

Commitment therapy that was not permitted during the study was:

- i). Carbamazepine
- i). Ketoconazole
- ii). Quinidine
- iii). Fluoxetine
- iv). Paroxetine

5.4.14.3 Receiving, Storage, Dispensing and Return

i). Receipt of Drug Supplies

Study drug (intervention) was supplied in bulk shipments by a pharmaceutical company. An inventory was performed after accepting the drug shipment. The study coordinator counted and verified that the shipment contained all the items mentioned in the supply. The investigator would notify the pharmaceutical company of any damage of the study drug.

ii). Storage

Stock study drug was stored in a locked cabinet in the research centre with climate control maintaining the temperatures within a range of 20°C to 25°C. Only the study coordinator and principal investigator have accessed to the study drug.

iii). Dispensing of Study Drug

The principal investigator or study coordinator would dispense the appropriate amount of study drug, according to the number of day of follow up. Subject compliance monitoring was conducted by doing pill counts at every study visit for all patients.

iv). Return of Study Drug

At the completion of the study, the final reconciliation of drug shipped, drug consumed and drug remaining was done. After appropriate

5 Aripiprazole and Methamphetamine-Induced Psychosis

accounting the pharmaceutical company was informed, the unused study drug was returned to the pharmaceutical company.

5.4.15. Conduct of study

i). Pre-test

A pre-test of the structured questionnaires was done on 10 patients who were attending the substances dependence clinic at UMMC. Some corrections were made to facilitate patients' understanding of the questionnaires.

ii). Training of study coordinator

The study coordinator was trained regarding the screening, recruitment and interviewing of the study patient for the baseline characteristics. She was also trained about the procedure in handling the study drug.

iii). Subject recruitment and screening

All inpatient and outpatient with psychotic symptom due to substance dependence were approached during this study. Some of the patients were recruited from the response of this study newspaper advertisement, and articles written up by principal investigator in newspaper pertaining to methamphetamine-induced psychosis. A Mini International Neuropsychiatric Inventory (M.I.N.I.) was administered to obtain DSM-IV diagnosis of methamphetamine dependence and to rule out Major Axis I psychiatric disorders. Urine toxicology was done and only patients with urine positive for methamphetamine during screening were included in this study.

5 Aripiprazole and Methamphetamine-Induced Psychosis

The patients were briefed on this study and written consent was obtained. Prior to the consent, patient was provided with a detailed information about aripiprazole, the rationale for why it was being studied, frequency of dosing, and length of treatment, potential benefits, side effects and risks, safeguards and emergency procedures. The collections of all laboratory specimens were described in detail, as the number and frequency of the research interviews and self-assessments. Patients were assured that their participation was voluntary and that withdrawal from the study would not jeopardize current or future treatment.

All medications taken by the patient for the 30 days prior to screening was documented. A face-to-face interview was conducted to collect primary data by using a structured questionnaire. Some secondary data pertaining to medical and surgical history were obtained from patient's case note. A complete physical examination was done including vital signs and weight and ECG was performed. The principal investigator confirmed and signed off on the inclusion and exclusion criteria on a case report form (CRF) prior to the patient formally recruited in the study or given study medication.

iv). Baseline visit

The patients were further evaluated with Positive and Negative Symptoms Scale (PANSS), Clinical Global Impression Scale– Severity of Illness (CGI-S), Amphetamine Withdrawal Questionnaire (AWQ), Brief Substance Craving Scale(BSCA), Abnormal Involuntary

5 Aripiprazole and Methamphetamine-Induced Psychosis

Movement Scale(AIMS), Barnes Akathasia Scale(BAS), Simpson Angus Scale(SAS) and Hospital Anxiety Depression Scale(HADS). A urine pregnancy test was conducted for female patients with childbearing capability.

v). Treatment

Eligible patients enrolled on Day 1 were treated with aripiprazole for 14 days. Aripiprazole was administered orally, once daily. The initial dose was given when the patient entered treatment; morning doses were preferred to give maximum drug concentration during daytime.

The initial dose was 5-10 mg. From Day 2 to Day 14, the dose of aripiprazole could be adjusted at 5 mg/day, 10 mg/day, or 15 mg/day at the investigator's discretion based on subject's clinical response and tolerability.

Lorazepam could be administered to treat agitation and anxiety, up to 6 mg/day, but not to be given in the morning before scheduled assessments. Zolpidem tartrate (up 10 mg/day was permitted to treat sleep disturbance throughout the study; all other sleep medications were prohibited. Antidepressant (SNRIs/SSRIs) was also allowed except for fluoxetine and paroxetine. Anticholinergics could be used to treat emergent EPS but prophylactic use was not permitted.

The introduction of other antipsychotic or psychoactive drugs during the study was prohibited, and must be discontinued at least 1 week before Day 1. Use of drugs that induce or inhibit the hepatic

5 Aripiprazole and Methamphetamine-Induced Psychosis

metabolising cytochrome 3A4 enzymes were also not permitted from 14 days prior to Day 1 until the end of treatment period. Depot and long-lasting antipsychotics must be stopped within at least two and preferably three dosing intervals prior to Day 1 and are prohibited during treatment period.

The patients were hospitalised if required for treatment and assessment based on the investigator's judgement. If patient was hospitalised, patient could be discharged from the hospital if the investigator believed that it was clinically appropriate to discharge the patient, and the patient could reasonably be expected to continue in the study on an outpatient basis.

vi). Follow-Up Evaluation

A follow-up evaluation was scheduled on day 4, 7 and 14 after the beginning of the study. If subjects could not attend the scheduled visit, subject was given appointment on the subsequent day.

At each follow-up evaluation, patients were assessed with Positive and Negative Symptoms Scale (PANSS) and Clinical Global Impression Scale-Severity of Illness (CGI-S). The methamphetamine withdrawal symptoms were assessed using Amphetamine Withdrawal Questionnaire (AWQ) Rating Scale and Brief Substance Craving Scale (BSCA). Any adverse event was recorded and patients were also evaluated with Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS) and Simpson Angus Scale (SAS). For Hospital Anxiety Depression Scale (HADS) the assessment was on day 14.

5 Aripiprazole and Methamphetamine-Induced Psychosis

If subjects experienced significant side effects from aripiprazole, the principal investigator would have the option to reduce the dose for aripiprazole, depending on the clinical interview. Acceptable dose reduction for aripiprazole was from one tablet per day (10 mg/day) to half tablets per day 5 mg/day. Upward titration following a dose reduction was allowed during the trial. Dose titration was documented in the study chart along with the clinical rationale. At the end of the study drug treatment period, study drug was discontinued without tapering.

The concomitant medications were reviewed. Finally pill count was done, the unused study drug was collected from the previous follow up and dispensed the new study drug. During the study visit, the study termination form was completed in case of discontinuation of patient from this study (Table 5.1).

5 Aripiprazole and Methamphetamine-Induced Psychosis

Table 5.2: Study visit plan for the treatment of aripiprazole among methamphetamine-induced psychosis patients

Visit	1	2	3	4	5
Visit Description	Screening	Treatment Started			Final visit
Day	< Up to – 1 day	1	4	7	14
Visit Window (\pm No. Days)					± 2
Informed consent	X				
Medical history	X				
Inclusion/Exclusion criteria	X	X			
Physical examination	X				X
Vital signs/Weight	X	X	X	X	X
Urinalysis/Drug Test	X				
PANSS	X	X	X	X	X
CGI-S	X	X	X	X	X
AWQ		X	X	X	X
BSCS		X	X	X	X
HADS		X			X
AIMS		X	X	X	X
SAS		X	X	X	X
BARS		X	X	X	X
Dispense study medication		X	X	X	X
Concomitant medication	X	X	X	X	X
Adverse events	X	X	X	X	X

vii). Subject Compliance Monitoring

The research coordinator conducted pill counts at the follow-up visit of all study patients. Unused amounts were documented. Proper drug

5 Aripiprazole and Methamphetamine-Induced Psychosis

dosing were reviewed with patients at each visit with clear instructions to take all study drugs as directed.

viii). End of medication evaluation

This evaluation was scheduled on the day 14 study drug treatment period. At this meeting, the following evaluations were completed:

- | | |
|----------|-------------------------|
| 1) PANSS | 6) SAS |
| 2) CGI-S | 7) AIMS |
| 3) AWQ | 8)HADS |
| 4) BSCS | 9) Physical examination |
| 5) BARS | 10) Vital signs |

5.4.16. Early withdrawal of subjects

Any patients experiencing a serious adverse event felt to be related to study drug were withdrawn from the study. Patients were also withdrawn if they required hospitalization for addiction or psychiatric treatment, received other psychotropic medications, or if discontinuation from the study was deemed by the principal investigator based on their best interest. Any patient withdrawing their consent to participate in the study or their authorization to use their protected health information was withdrawn from the study. Patients discontinued from the clinical trial were given appropriate treatment referrals to the outpatient psychiatric clinic, UMMC. Patients were instructed to return all unused medications. For the early withdrawal, patients had all final assessments that originally were scheduled for

5 Aripiprazole and Methamphetamine-Induced Psychosis

the end of study visit. Patients withdrawn might be replaced, at the discretion of the principal investigator.

All patients were included in the final study analyses. Patients were not dropped from any study activities unless they requested not to be contacted or could not be located for the 1-week follow-up assessment. Patients were informed at the consent session that treatment might be discontinued due to:

- i). Intolerable side effects
- ii). Development or exacerbation of psychiatric symptoms necessitating inpatient admission or a more aggressive therapeutic intervention than was provided by the protocol
- iii). Methamphetamine or other substance abuse necessitating inpatient admission or a more aggressive treatment than was provided by the protocol
- iv). Clinical deterioration for any reason or any clinical status that necessitates inpatient admission
- v). Incarceration for more than 1 week
- vi). Failure to attend 2 consecutive outpatient evaluation visits
- vii). Failure to provide laboratory specimens

Reasons why patients discontinued from the clinical trial were documented on the Study Termination Form, along with any referrals

that were made. A final safety evaluation was conducted as soon as possible on all patients who have been discontinued from the study.

5.4.17. Safety and Adverse Events

Recording of Adverse Events

During the research evaluation visit, the patient was asked on adverse events through specific questioning and by examination. Information on all adverse events was recorded immediately in the case report form (CRF). Each adverse event was followed up until resolution or stabilization has been achieved.

In the case of the occurrence of serious adverse event (SAE), it was followed up to determine the final outcome. Any serious adverse event that occurred after the study period was considered possibly related to the study drug, was recorded and reported immediately.

5.4.17.1 Reporting of Serious Adverse Events

Ethic Committee (EC) Notification by Principle

Investigator

A serious adverse event must be reported to the EC within 24 hours (one working day) of the event. The principal investigator would keep a copy of the SAE form in the file. Within the following 48 hours, the principal investigator would provide further information and progress on the serious adverse event to the EC.

In the SAE form, the following information should be provided:

5 Aripiprazole and Methamphetamine-Induced Psychosis

- i). Study identifier
- ii). Subject number
- iii). A description of the event
- iv). Date of onset
- v). Current status
- vi). Whether study treatment was discontinued
- vii). The reason why the event was classified as serious
- viii). Principle investigator assessment of the association between the event and study drug

5.4.17.2 Medical Monitoring

The principal investigator was responsible to oversee the safety of the study. This safety monitoring would include careful assessment and appropriate reporting of adverse events. Medical monitoring would include a regular assessment of the number and type of serious adverse events.

6.4.14.5 Protection of Subjects

Additional procedures would be conducted to protect the safety of the study patients. Potential patients would be screened for medical illnesses that would preclude the use of aripiprazole. Patients selected for the study would be evaluated for AE while receiving study drug. Venipuncture was carried out with good aseptic technique by an

5 Aripiprazole and Methamphetamine-Induced Psychosis

experienced nurse or physician. Before initiating study medication, a physical examination, ECG and a urine pregnancy test (if female of childbearing capability) were performed. Patients were given a 24-hour emergency number form them to call if necessary. The principle investigator would follow all patients who were discontinued due to a serious AEs until the AE resolved and become completely stable, unless a referral to another physician or specialist was clinically indicated or requested by the patient.

5.4.18. Data Handling and Record Keeping

i). Data Management

The data were checked before ending each interview session and before compilation to ensure completeness. If missing data was found, the patient will be contacted through telephone. Raw data obtained were coded and entered into Statistical Package for Social Sciences (SPSS) Version 16.0. The data were summarized by running frequency distributions and simple descriptive statistics (means and standard deviations). Cleaning for double entry and outliers before analysis was done.

ii). Confidentiality

Information about study patients was kept confidential and managed according to the requirements of the EC.

iii). Source Data and Case Report Form

Source data was all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data were contained in source documents such as hospital records, clinic charts, laboratory results, pharmacy dispensing records, recorded data from automated instruments, microfilm or magnetic media, x-rays, subject files, records kept at the pharmacy, at the laboratories, at medical record department and other related documents.

The study case report form (CRF) was the primary data collection instrument for the study. All data requested on the CRF were recorded and all missing data were explained. "N/D" was written if a space on the CRF was left blank because the procedure was not done or the question was not asked. "N/A" was written if the item was not applicable to the individual case. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line was drawn through the incorrect entry and the correct data was entered above it. All such changes were initialed and dated.

5.4.19. Statistical Analysis

i). Univariate analyses

Descriptive statistics were used to summarize demographic variables, past medical and surgical history, history of drug use and adverse

5 Aripiprazole and Methamphetamine-Induced Psychosis

events. For nominal independent variables, they were described in the form of frequencies and percentages. For continuous independent variables, they were summarized and described as means, standard deviations and median.

ii). Bivariate analysis

The paired *t*-test was used to examine changes in PANSS and subscale, CGI-S, AWQ, BSCS, BARS, SAS and AIMS scores, by pairing scores at i) baseline before initiating aripiprazole and those at day 4, ii) baseline before initiating aripiprazole and those at day 7, and iii) baseline before initiating aripiprazole and those at day 14. The paired *t*-test HADS rating scale was between baseline before initiating aripiprazole and those at day 14. An alpha level of significance 0.05 was set for all analyses.

iii). Multivariate Analysis

To examine changes in PANSS total, CGI-S, AWQ and BSCS scores over time we employed mixed-model repeated measures (MMRM). The dependent variables were the total PANSS total, CGI-S, AWQ, BSCS scores. Time (four levels, ie, at baseline and at day 4, 7 and 14) were fitted as main effects for MMRM.

5.5 Results

Patients

In total, 145 patients were screened and 73 were eligible. However only 49 agreed to participate and proceeded to receive the study medication. Out of the 49 patients who received the study medication, 8 (16.3%) discontinued treatment early due to: loss to follow up (n=4), adverse event/akathisia (n=2), withdraw consent (n=1) and detention by the police (n=1). Forty-one patients completed the study (Figure 5.3).

There were more male than female patients in the study (46 vs 3); Malay and Chinese patients accounted for more than 85.7% of subject population. Mean age of patients was 34.2 ± 8.4 (SD) years. Only 38.8% of the patients were married, while the rest were either single or divorced. Majority of the patients received education up to secondary level and have fulltime job. The mean income for the patients was RM 3,310 per month (Table 5.3).

Based on the DSM-IV Diagnosis Criteria, all the subject fulfilled the criteria for methamphetamine dependence. Three patients (6.1%) had medical history; two were in the past being treated for pneumonia and hepatitis C respectively, and one was under current medication for the condition of HIV. Two patients (4.1%) had surgical history in the past but were not under any current medication.

5 Aripiprazole and Methamphetamine-Induced Psychosis

The key baseline characteristics, including efficacy and safety baseline measurements of PANSS scores CGI scores, HADS scores, BSCS scores, AWQ scores, BARS scores, SAS scores and AIMS scores of study subjects were summarized in Table 5.4.

Figure 5.3 Disposition of patients in the treatment of aripiprazole for methamphetamine-induced psychosis

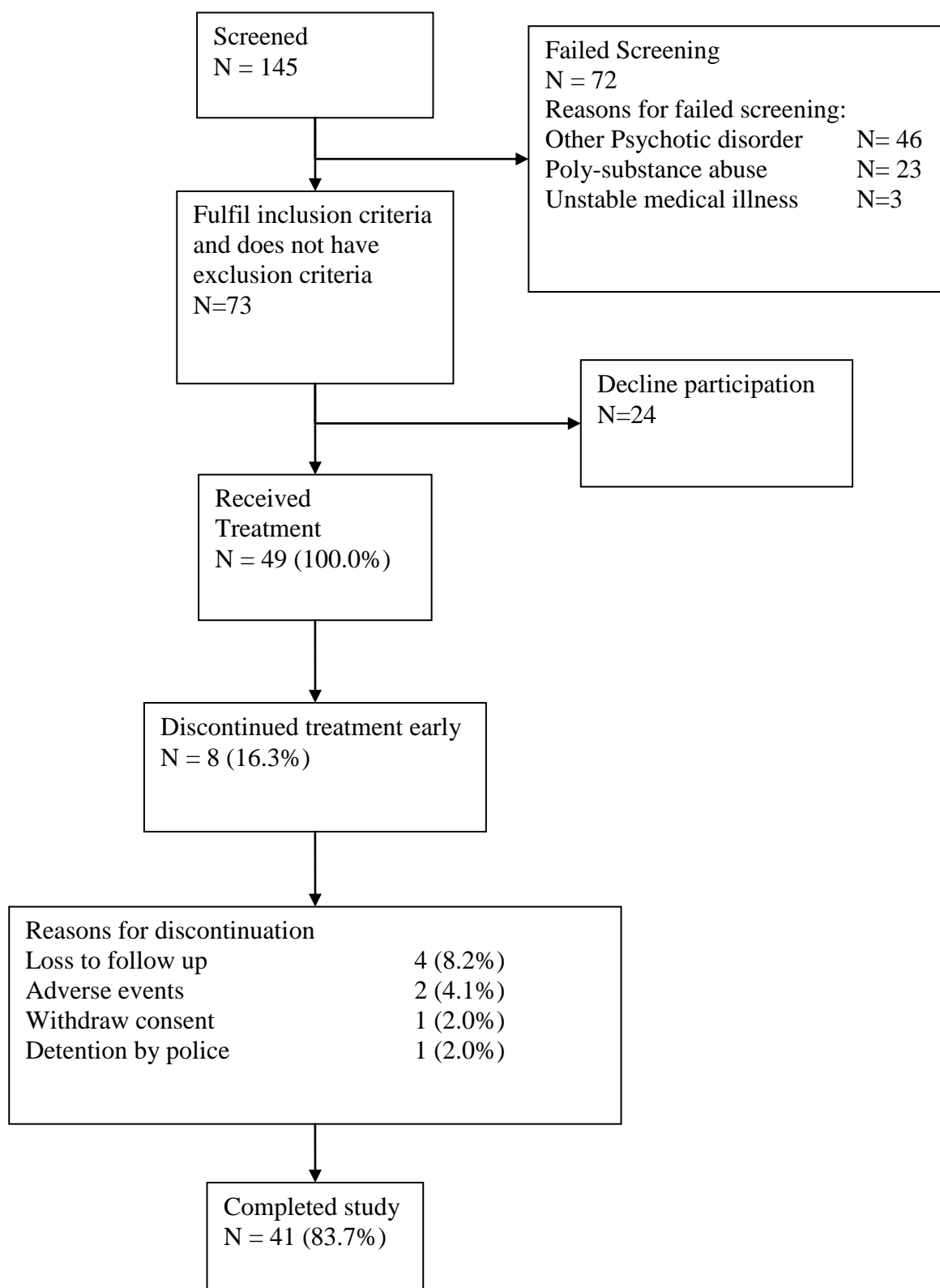


Table 5.3: Socidemographic and drug history of methamphetamine-induced psychosis subjects

Demographic characteristics	N=49
Sex, n (%)	46 (93.9)
Male	3 (6.1)
Female	
Age, mean years (SD)	34.2 (8.4)
Race, n (%)	
Malay	30 (61.2)
Chinese	12 (24.5)
Indian	7 (14.3)
Marital Status, n (%)	
Married	19 (38.8)
Single	24 (48.9)
Divorced	6 (12.3)
Education Level, n (%)	
Tertiary	9 (18.4)
Secondary	37(75.5)
Primary	3(6.1)
Employment Pattern, n (%)	
Full Time Job	38 (77.6)
Part Time Job	1 (2.0)
Student	3 (6.1)
Unemployed	7 (14.3)
Duration of Employment, mean years (SD)	43.6 (51.4)
Income, mean Ringgit Malaysia (SD)	3,310.0 (4,079.3)
Past Medical/Surgical History, n (%)	
Medical history (Hep C, HIV, Pneumonia)	3(6.1%)
Surgical history (Kidney stone, MVA)	2(4.1%)
Methamphetamine Use History	
Onset Age, mean years (SD)	29.0 (9.0)
Duration Used, mean years (SD)	5.6 (4.4)
Amount Used Monthly, mean Ringgit Malaysia (SD)	1,386.1 (1,846.8)
Route of Use, n (%)	
Oral	5 (10.2)
Nasal	14 (28.6)
Smoking	22 (61.2)

Table 5.4: Baseline characteristics of efficacy and safety measures

Baseline efficacy measurements, mean (SD)	
PANSS-Total score	79.2 (13.7)
PANSS-P score	21.7 (5.2)
PANSS-N score	16.8 (3.6)
PANNS-General psychopathological score	40.6 (7.2)
CGI-S score	4.3(0.5)
AWQ score	17.0 (8.8)
BSCS score	6.4(3.9)
HADS – Depression score	4.5 (5.0)
HADS – Anxiety score	4.5 (4.9)
Baseline EPS symptoms, mean (SD)	
AIMS score	0
BARS score	0.1(0.5)
SAS score	0

5 Aripiprazole and Methamphetamine-Induced Psychosis

Mean dose of aripiprazole

The mean dose of aripiprazole was 7.0 ± 2.9 mg on day 1, 7.2 ± 3.3 mg on day 4, 9.2 ± 3.1 mg on day 7 and 9.4 ± 3.6 mg on day 14.

Concomitant medications

None of the patients received medication prior to the study. All the patients were neuroleptic naïve.

A total of 13 (26.5%) patients received concomitant therapies during the study. The most common concomitant therapies used was lorazepam (n=9, 18.4%). Lorazepam were given for akathisia (n=4, 8.2%), agitation (n=3, 6.1%) and insomnia (n=2, 4.1%). 2 patients (4.1%) were given zolpidem for insomnia and 2 patients (4.1%) were given escitalopram for depression.

Efficacy

Efficacy analyses were based on the intention-to-treat (ITT) population.

Primary efficacy variable

The primary variable was the change from baseline in PANSS-Total score to the end of treatment (day 14) where baseline was defined as the day subject first received study medication (day 1, visit 2). Other primary variables include change from baseline in PANSS positive subscales, PANSS negative subscales, PANSS general psychopathology subscales and CGI-S to the end of treatment (day 14).

5 Aripiprazole and Methamphetamine-Induced Psychosis

Results showed that there was a steady decline in the mean PANSS-Total score over the course of the study, with a mean reduction of 27.6 ± 21.4 point ($p < 0.05$, 95% CI [- 34.8, -20.4] from baseline at day 14 (Table 5.7), thus indicating a statistically significant improvement in patients after receiving aripiprazole. For the CGI scale there were also significant decline with the mean reduction of 2.0 ± 1.2 point ($p < 0.05$, 95% CI – 2.4, -1.6] from baseline at day 14.

Similar statistically significant reduction can also be seen in all the PANSS subscales scores from baseline at day 14 (Table 5.7). Statistically significant improvement were also noted in PANSS-Total, all PANSS subscales and CGI-S scores from baseline at day 4 (Table 5.5) and at day 7 (Table 5.6).

Secondary efficacy variables

The secondary efficacy measures were changed from baseline in the AWQ score, BSCS score and HADS score.

Results showed that there was a statistically significant decline in the mean AWQ score over the course of the study, with a mean reduction of -8.5 ± 9.6 point ($p < 0.05$, 95% CI [-11.8, -5.2] from baseline at day 14 (Table 5.7). For the BSCS scale, the mean reduction was 2.8 ± 3.8 point ($p < 0.05$, 95% CI -4.0, -1.5] from baseline at day 14, thus indicating a statistically significant improvement in patients after receiving aripiprazole.

5 Aripiprazole and Methamphetamine-Induced Psychosis

The HADS anxiety subscales (Table 5.7) showed a statistically significant improvement with a mean reduction of 3.9 ± 4.8 points ($p < 0.05$, 95% CI -5.6, -2.4). Similarly, the HADS depression subscales showed a statistically significant improvement with a mean reduction of 3.5 ± 5.5 points ($p < 0.05$, 95% CI -5.4, -1.7).

Statistically significant reductions in mean score were also noted for the AWQ and BSCS scales from baseline at day 4 (Table 5.5), and day 7 (Tables 5.6).

Table 5.5: Primary and secondary efficacy variables – Changes from baseline at Day 4*

Variables	Baseline score \pm SD	Day 4 score \pm SD	Mean \pm SD	95% Confidence interval
Primary efficacy				
PANSS-Total	79.2 \pm 13.7	71.7 \pm 12.3	-7.4 \pm 15.7	- 12.7, -2.2
Secondary efficacy				
PANSS-P	21.7 \pm 5.2	19.0 \pm 4.1	-2.7 \pm 5.1	-4.4, -1.0
PANSS-N	16.8 \pm 3.6	15.5 \pm 3.6	-1.3 \pm 2.8	-2.2, -0.4
PANSS-G	40.6 \pm 7.2	37.2 \pm 6.7	-3.4 \pm 8.5	-6.2, -0.5
CGI-S	4.3 \pm 0.5	3.8 \pm 0.9	-0.5 \pm 1.0	- 0.8, -0.2
AWQ	17.0 \pm 8.8	15.0 \pm 8.8	-15.0 \pm 8.8	-3.8, -0.3
BSCS	6.4 \pm 3.9	5.6 \pm 3.9	5.6 \pm 3.9	-1.5, -0.1

**All changes from baseline at Day 4 were statistically significant with $p < 0.001$. T-test was used to compare mean changes from baseline for PANSS total score, PANSS subscales scores, CGI-S score, AWQ score and BSCS score*

Table 5.6: Primary and secondary efficacy variables – Changes from baseline at Day 7*

Variables	Baseline score \pm SD	Day 7 score \pm SD	Mean \pm SD	95% Confidence interval
Primary efficacy				
PANSS-Total	79.2 \pm 13.7	61.7 \pm 11.9	-17.4 \pm 17.1	-23.1, - 11.7
Secondary efficacy				
PANSS-P	21.7 \pm 5.2	15.7 \pm 3.8	-6.0 \pm 5.9	-8.0, -4.0
PANSS-N	16.8 \pm 3.6	13.5 \pm 3.6	-3.2 \pm 3.7	-4.5, -2.0
PANSS-G	40.6 \pm 7.2	32.5 \pm 6.2	-8.1 \pm 8.9	-11.0, -5.1
CGI-S	4.3 \pm 0.5	2.9 \pm 0.8	-1.4 \pm 1.1	- 1.8, -1.0
AWQ	17.0 \pm 8.8	11.5 \pm 7.8	5.6 \pm 8.2	-8.3, -2.8
BSCS	6.4 \pm 3.9	4.5 \pm 3.3	1.9 \pm 2.5	-2.7, -1.0

**All changes from baseline at Day 7 were statistically significant with $p < 0.001$. T-test was used to compare mean changes from baseline for PANSS total score, PANSS subscales scores, CGI-S score, AWQ score and BSCS score*

Table 5.7: Primary and secondary efficacy variables – Changes from baseline at Day 14*

Variables	Baseline score \pm SD	Day 14 score \pm SD	Mean \pm SD	95% Confidence interval
Primary efficacy				
PANSS-Total	79.2 \pm 13.7	51.6 \pm 14.7	-27.6 \pm 21.4	- 34.8, -20.4
Secondary efficacy				
PANSS-P	21.7 \pm 5.2	12.3 \pm 4.4	-9.5 \pm 7.0	-11.8, -7.1
PANSS-N	16.8 \pm 3.6	11.2 \pm 3.3	-5.6 \pm 4.7	-7.2, -4.0
PANSS-G	40.6 \pm 7.2	27.8 \pm 7.7	-12.8 \pm 10.9	-16.4, -9.2
CGI-S	4.3 \pm 0.5	2.3 \pm 1.0	-2.0 \pm 1.2	- 2.4, -1.6
AWQ	17.0 \pm 8.8	8.5 \pm 8.0	-8.5 \pm 9.6	-11.8, -5.2
BSCS	6.4 \pm 3.9	3.6 \pm 3.4	-2.8 \pm 3.8	-4.0, -1.5
HADS – Depression	8.1 \pm 5.0	4.6 \pm 4.5	-3.5 \pm 5.5	-5.4, -1.7
HADS – Anxiety	8.8 \pm 4.9	3.9 \pm 4.8	-3.9 \pm 4.8	-5.6, -2.4

**All changes from baseline at Day 14 were statistically significant with $p < 0.001$. T-test was used to compare mean changes from baseline for PANSS total score, PANSS subscales scores, CGI-S score, AWQ score, BSCS score and HADS subscales scores.*

Table 5.8: Mixed-model repeated measures (MMRM) analyses of primary and secondary efficacy at baseline, day 4, day 7 and day 14.

Variables	Baseline score \pm SD	Day 4 score \pm SD	Day 7 score \pm SD	Day 14 score \pm SD	F	p
Primary efficacy						
PANSS-Total	79.2 \pm 13.7	71.7 \pm 12.3	61.7 \pm 11.9	51.6 \pm 14.7	45.569	<0.05
Secondary efficacy						
CGI-S	4.3 \pm 0.5	3.8 \pm 0.9	2.9 \pm 0.8	2.3 \pm 1.0	42.223	<0.05
AWQ	17.0 \pm 8.8	15.0 \pm 8.8	11.5 \pm 7.8	8.5 \pm 8.0	15.473	<0.05
BSCS	6.4 \pm 3.9	5.6 \pm 3.9	4.5 \pm 3.3	3.6 \pm 3.4	4.395	<0.05

Safety and tolerability

Adverse events (AE)

Aripiprazole was generally well tolerated during the study. Adverse events were reported in 10 (20.4%) patients during the study period, after 14 days of study exposure.

The reported AEs were akathisia, insomnia, agitation, sedation and depression (Table 5.9). Most AEs were mild to moderate in intensity. Akathisia was rated as moderate in 2 patients and mild in 2 other patients. Insomnia was rated as mild in all 4 patients. Agitation was rated as mild in all 3 patients. Sedation and depression were all rated as moderate. The AEs of akathisia and insomnia were judged by the investigator to be associated to the study medication. Two patients discontinued from the study due to akathisia. There was no serious adverse event during the study period.

Table 5.9: Number (%) of Patients reporting Adverse Events – Safety Population

	All Subjects (N=49)
Study exposure, mean (min, max) days	11.7 (4,14)
Number of patients experienced AE, n (%)	10 (20.4%)
ADVERSE EVENT, n (%)	15 (30.6%)
Akathisia	4 (8.1%)
Insomnia	4 (8.1%)
Agitation	3 (6.1%)
Sedation	2 (4.1%)
Depression	2 (4.1%)

Table 5.10: Primary Safety variables – Changes from baseline at Day 4, 7 and 14

Variables	Baseline score \pm SD	Day 4 \pm SD	Day 7 \pm SD	Day 14 \pm SD
BARS	0.7 \pm 0.5	0.2 \pm 0.8	0.3 \pm 1.2	0.7 \pm 2.1
SAS	0	0	0	0
AIMS	0	0	0	0

P > 0.05 for all safety data

Extrapyramidal side effects

There were no significant changes in BARS, SAS, AIMS scores between baseline and day 4, 7 and 14 (Table 5.10).

5.6 Discussion

The present study can be considered the first pilot study in Malaysia to investigate the safety and potential efficacy of aripiprazole in treating individuals with methamphetamine-induced psychosis. While the number of patients included in the study was small (49 patients), the patients were reasonably homogenous in terms of: i) all patients had methamphetamine induced psychosis, without any history of other psychotic disorders, and ii) as such, those patients were never exposed to any antipsychotics before (i.e. neuroleptic naïve patients).

However, it should be noted that the subjects in the present study do not represent a general population of methamphetamine abuse, including habitual users. Thus, the present study has a methodological limitation, which is that only methamphetamine dependent with psychotic symptoms was examined.

Our data indicated moderate to severe psychotic symptoms among the subjects at baseline. The mean baseline scores on the PANSS total score and the CGI scores were above the cut-off points. Following the treatment with aripiprazole for 2 weeks, statistically and clinically significant reductions across the assessment instruments used in this study were noted. The reduction in symptoms were noted as early as in day 4 and maintained until the end of the study (day 14). Our data suggests that aripiprazole may be a potentially effective pharmacological treatment for methamphetamine psychosis. We believe that these results may have to do with the efficacy of

5 Aripiprazole and Methamphetamine-Induced Psychosis

aripiprazole relating to the positive and negative symptoms, as well as the associated depressive and anxiety symptoms. It is not clear why aripiprazole may have a positive effect on symptoms of depression and anxiety. Aripiprazole have an effect on both the dopaminergic and serotonergic systems. Both of these neurotransmission pathways have been implicated in both depression and anxiety, and agents that have an effect on these systems may ameliorate these symptoms(Stein *et al.*, 2002). The effects of aripiprazole may be given rise from its activity at the serotonin 1A (5-HT^{1A}) receptor (Carli *et al.*, 1993, Collinson and Dawson, 1997), and its partial agonist and dopaminergic stabilising qualities(Adson *et al.*, 2005).

Our study also showed that aripiprazole might have treatment effect on methamphetamine withdrawal syndrome and cravings. In our study subjects, treatment with aripiprazole led to a significant decline in AWQ and BSCS scores, indicating a reduction the severity of drug withdrawal syndrome and substance cravings. This effect began as early as day 4, suggesting a rapid onset of action of aripiprazole.

This particular finding of our study substantiates the results from an earlier study by Beresford (Beresford *et al.*, 2005) in which treatment with aripiprazole significantly alleviate cocaine and alcohol cravings in schizophrenia subjects. In their prospective, 8-week, open-label study involving poorly compliant schizophrenia patients with cocaine dependence, treatment with aripiprazole led to a significant decline in the cocaine craving scores (as measured by BSCS) and substance use, as reflected in a significant drop in positive urine tests after 2

5 Aripiprazole and Methamphetamine-Induced Psychosis

weeks. Psychosis scores in those patients declined, corresponding to the decline in cocaine craving. Both our study and theirs suggests possible aripiprazole effects in lowering the desire for and the use of substance in patients with co-morbid psychiatric disorder, including subjects with methamphetamine induced psychosis.

In our study, the initial dose of aripiprazole used was 5-10mg mg/day, and was gradually titrated to higher doses of 10 mg/day or 15 mg/day over the study period. The doses used in our patient population appeared to be effective, as reflected in the significant improvements across the efficacy parameters. However, a double-blind study by Newton (Newton *et al.*, 2008) to evaluate the effects of aripiprazole treatment on abstinence-related craving and cue-induced craving among non-treatment seeking, methamphetamine dependent users, reported that aripiprazole given at 15 mg is unlikely to be efficacious for the treatment of methamphetamine dependence. Whether this discrepancy is purely due to study design or could be attributed to a genetic reason (e.g. different ethnicities have different therapeutic dose of aripiprazole) remains to be ascertained through further research.

Our study also showed that aripiprazole was well tolerated in most patients and safe to be used in antipsychotic-naïve patients, as shown by the low incidence of adverse effects associated with aripiprazole and the high retention rate (83.6%) in this study.

The reported AEs (akathisia, insomnia, agitation, sedation and depression) were in agreement with the most common adverse effects

5 Aripiprazole and Methamphetamine-Induced Psychosis

found in other clinical trials of aripiprazole in schizophrenia (Kern *et al.*, 2006, Kane *et al.*, 2002). All the AEs were of mild to moderate severity.

There was a non-significant increase in BARS, mainly due to four patients who reported akathisia. Akathisia is not uncommon with aripiprazole. While second-generation antipsychotic drugs have been reported to cause fewer incidences of extrapyramidal symptoms (EPSs) than typical antipsychotic drugs, AEs such as akathisia have been observed with atypical antipsychotic drugs (Iqbal *et al.*, 2007, Kane *et al.*, 2009).

Aripiprazole is known to have a relatively low rate of EPSs and a low propensity for weight gain and prolactin-related adverse events (Chrzanowski *et al.*, 2006, Marder *et al.*, 2003, Kolotkin *et al.*, 2008, Findling *et al.*, 2008). This may offer an advantage in terms of treatment compliance, especially when patients have to be put on a longer duration of treatment.

While no incidence of tardive dyskinesia (TD) was reported in our study, aripiprazole has been implicated as a cause of TD in patients never exposed to other dopamine receptor-blocking agents. In a recent review of studies using comparable doses of antipsychotics, the annualised incidence of TD was estimated to be 3.9% for atypical antipsychotics compared with 5.5% for conventional antipsychotics (Correll and Schenk, 2008). For this reason, caution should be exercised when aripiprazole is used in neuroleptic-naïve patients.

5 Aripiprazole and Methamphetamine-Induced Psychosis

Currently, the data on efficacy of antipsychotics in methamphetamine-induced psychosis is very limited. Only one small randomised controlled trial (Leelahanaj *et al.*, 2005) involving 58 participants has been published. The study compared the efficacy and tolerability of two antipsychotic drugs, olanzapine and haloperidol, in treating amphetamine-induced psychosis. Both drugs at clinically relevant doses were efficacious in resolving psychotic symptoms associated with amphetamine use.

In Malaysia, there has been no similar study conducted. Whether the limited evidence from our current study using aripiprazole can be applied for all methamphetamine psychotic patients is not yet known. The treatment of methamphetamine-induced psychosis with aripiprazole should be further investigated. Further studies of methamphetamine-induced psychotic symptoms and the prevalence of relapse to psychosis in the presence of methamphetamine are also crucial for developing study designs appropriate for treatment studies of methamphetamine psychosis.

Although our current study is hampered by a small sample size, the responses of our study subjects to the pharmacotherapy of aripiprazole are noteworthy. We foresee to obtain more defining and valuable data from an extension of this study that will recruit more subjects and be conducted over a longer treatment period.

Limitation and Errors

i). Adequacy of Sample Size

The required sample size was 33, when the calculated study sample was based on 80% power of the study; the difference of mean was 10 and standard deviation of 20. The actual completed study subjects were 41 and have maintained the power of study.

ii). Conduct of study

This was an open label single arm intervention study. The efficacy outcomes measured were not superior as randomized double blind study.

iii). Representative and Generalisation

The findings of this study could only generalize with caution because the study population was from the inpatient and outpatient clinic located in a hospital in Kuala Lumpur. The study population differs from the patients in the community because of the treatment seeking behavior. To make generalized inferences of the findings of this study to the methamphetamine dependence induced psychosis patients in community would be inappropriate because the setting in this study had introduced selection bias.

For a better generalization of the findings, it would be ideal to conduct a community survey. Unfortunately, such a study is not feasible to conduct due to the legal implication.

iv). Instruments of the study

All the scales have been used widely in this country however until now, there was no paper being published regarding the validation of the scales in the local population.

v). Comparing Findings With Other Studies

Comparison of the findings of this study to other studies may be inaccurate, although other studies examined the same variables, but the inclusion and exclusion criteria used to identify subjects or sampled population could differ, or study could be conducted with difference study design.

5.7 Conclusions

This 2-week, open-label study shows that aripiprazole given once-daily at 10 mg/day to 15 mg/day improved the psychotic symptoms associated with methamphetamine use, as measured with PANSS scores. In addition, the treatment also improved the depressive and anxiety symptoms, as well as reduced drug withdrawal symptoms and substance craving severity. The treatment was generally well tolerated with mild to moderate AEs comparable to other aripiprazole studies. Aripiprazole may be a potential pharmacotherapy for methamphetamine-induced psychosis, but its efficacy needs to be confirmed by larger and longer-duration trials.

7 Overall Conclusions and Recommendations

Chapter SIX: Randomized Placebo-Controlled Trial of the Safety and Efficacy of Aripiprazole in the Treatment of Methamphetamine Dependence Patients

6.1 Abstract

Introduction: There is a great need in the treatment of methamphetamine dependence. The goals of methamphetamine dependence treatment are to reduce further drug use, improve the patient's ability to function, minimize the medical and social complications of drug abuse and dependence, and ultimately to achieve lasting abstinence.

Objectives: The objective of this study was to determine the efficacy and safety of aripiprazole among methamphetamine dependence patients.

Methodology:

Design: This was a double blind randomized controlled trial.

Setting: Patients were recruited from the inpatient psychiatric wards and outpatient psychiatric clinic in University Malaya Medical Centre (UMMC), Kuala Lumpur.

Patients: The study population included male or female with a current Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnosis of methamphetamine dependence.

7 Overall Conclusions and Recommendations

Intervention: Eligible patients were treated with the initial dose of 10 mg Aripiprazole. From day 2 to day 56, aripiprazole was flexible dosed (5-10mg/day) at the discretion of the treating psychiatrist.

Measures: The primary outcome measure was to determine the efficacy of aripiprazole in maintaining of abstinence and retention among methamphetamine dependence patients. Other scales included in this study were the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression scale (CGI), the Brief Substance Craving Scale (BSCS), Barnes Akathisia Scale (BAS), Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS) and Hospital Anxiety Depression Scale (HADS). Intention-to-treat was used for the data analysis. Generalized Estimating Equation (GEE) and Mixed-Effects Model Repeated-Measures (MMRM) analysis was utilized to examine changes in outcome measures over time with the treatment aripiprazole.

Results: Nineteen patients were randomized to aripiprazole and 18 to placebo. About 84.2% of participants randomized to aripiprazole completed the 8 weeks study compared to only 50% of the placebo group completed the study ($p < 0.05$). There was a statistically significant difference between groups in the amount of time spent in treatment ($p < 0.05$), with those given aripiprazole retained for an

7 Overall Conclusions and Recommendations

average of 48.7 days (± 4.0) compared with only 37.1 days (± 5.0) for the placebo group. The survival curves results showed that participants in the aripiprazole group were less likely to drop out of the study than those in the placebo group. The difference was statistically significant ($p = 0.02$, $X^2 = 5.3$). Psychotic symptoms as measured by PANSS and CGI were decreased among participants who were randomized to aripiprazole treatment but those who were randomized to placebo showed an increased in the total PANSS and CGI score ($p < 0.05$). However there were no statistically significant effects for aripiprazole relative to placebo on methamphetamine use verified by urine drug screen. The generalised estimation equation analysis showed that the difference between aripiprazole and placebo in the urine analysis was not significant ($p = 0.41$). Aripiprazole treatment was not associated with any serious adverse event. Adverse events were generally mild and consistent with known pharmacological effects.

Conclusion: Aripiprazole was no more effective than placebo in maintaining abstinence from methamphetamine use. However, it facilitated treatment retention and reduced the occurrence of psychotic symptoms in this study population. Aripiprazole was generally safe and well tolerated. It might have a role in the treatment of methamphetamine dependence with psychotic symptoms.

Keywords: Randomized controlled trial, Placebo Controlled, Methamphetamine dependence, Aripiprazole, Psychosis, Safety, Efficacy

7 Overall Conclusions and Recommendations

6.2 Introduction

Treatment of methamphetamine dependence

Methamphetamine dependence, and drug dependence in general, is a treatable brain disease. The goals of drug dependence treatment are to reduce further drug use, improve the patient's ability to function, minimize the medical and social complications of drug abuse and dependence, and ultimately to achieve lasting abstinence (Kay-Lambkin *et al.*, 2010).

Managing methamphetamine dependence, as well as to recover from it, does not involve a brief detoxification and discharge, but a long-term process to help individuals free themselves from illicit substance use (Bruce, 2000). Through tailored treatments many people with drug use disorders are able to recover and lead productive lives.

Psychosocial and behavioural approaches are currently the primary treatments for methamphetamine dependent individuals. Medications may also be used alone or in combination with behavioural therapy. Meanwhile, research continues to investigate the potential roles of replacement pharmacotherapies in drug dependence.

Psychosocial and behavioural therapies

At present, the most effective treatments for ATS dependence addiction are behavioural therapies (Nhduh, 2005), such as cognitive behavioural and contingency management interventions, which have been successfully used in treating cocaine addiction (Rawson *et al.*,

7 Overall Conclusions and Recommendations

2002b) and may have some benefit in treating methamphetamine addiction.

i). Cognitive behavioural therapy

The Matrix Model is an individualized outpatient regimen that has been used successfully to treat patients who abuse stimulants (Shoptaw *et al.*, 1994, Rawson *et al.*, 2004). It is a comprehensive 16-week behavioural treatment approach that combines behavioural therapy, family education, individual counselling, 12-step support, relapse analysis, urine testing, and encouragement for non-drug-related activities. The Center for Substance Abuse Treatment Methamphetamine Treatment project (Rawson *et al.*, 2004) has shown that the Matrix approach is effective in reducing methamphetamine abuse, where patients were more likely to stay in treatment, complete treatment, and more likely to have negative methamphetamine urine test results compared with those who received standard outpatient treatment.

ii). Contingency management program

Contingency management rewards methamphetamine-dependent patients when they engage in treatment and maintaining abstinence (e.g submitting drug-free urine samples). This intervention has also been shown to be effective by reducing methamphetamine abuse and high-risk sexual behaviour (Shoptaw *et al.*, 2005).

7 Overall Conclusions and Recommendations

In short, behavioural therapies help patients stay on to the treatment process, modify their attitudes and behaviours related to drug abuse, and increase healthy lifestyle skills (Kay-Lambkin *et al.*, 2010). If patients are on medications, behavioural treatments can also help enhance the effectiveness of the medications and help them stay in treatment longer (Kay-Lambkin *et al.*, 2010).

iii). Pharmacotherapy

Besides specific behavioural therapies, medications can be used to target different aspects along the treatment process. Medications can be used to help re-establish normal brain function, and to ebb cravings and prevent relapse throughout the treatment process (Kay-Lambkin *et al.*, 2010).

However, there is currently no approved medication by the Food and Drug Administration (FDA) or the Malaysian Drug Authority to be used in the treatment of methamphetamine dependence. All the treatments that are being used at this moment are off label usage.

Treating withdrawal symptoms and addiction

The overall therapeutic process of drug dependence often begins with detoxification, followed by treatment and relapse prevention (Kay-Lambkin *et al.*, 2010). During the detoxification stage, withdrawal symptoms such as intense craving, fatigue, dysphoric mood, anhedonia, depression and agitation, are common among methamphetamine users (Mcgregor *et al.*, 2005). These symptoms

7 Overall Conclusions and Recommendations

may last several days to weeks after cessation or reduction in heavy and prolonged use of methamphetamine, and may present a critical factor leading to relapse of methamphetamine use.

Medications play a role here by helping to suppress the withdrawal symptoms (i.e. medically assisted withdrawal). This can be very important in the initiation of treatment to prevent relapse.

At present, no available treatment has been demonstrated to be effective in the treatment of methamphetamine withdrawal. In clinical practice, treatment for cocaine withdrawal has been recommended for the management of ATS withdrawal (Cretzmeyer *et al.*, 2003) despite the difference in the pharmacodynamic and pharmacokinetic properties of these two substances.

While there are already medications available for opioid and tobacco addiction, evidence on treatment for ATS dependence is scarce.

A Cochrane review concluded that fluoxetine and imipramine have very limited benefits for amphetamine dependence and abuse (Srisurapanont *et al.*, 2001a). While fluoxetine may decrease craving in short-term treatment, imipramine may increase duration of adherence to treatment in medium-term treatment. Apart from these, no other benefits, in particular proximal benefits can be found.

While one small randomised controlled trial found bupropion decreased subjective effects of methamphetamine and cravings in a laboratory setting (Newton *et al.*, 2006), risperidone was shown to be well

7 Overall Conclusions and Recommendations

tolerated and associated with decreased methamphetamine use in an open-label pilot study (Meredith *et al.*, 2007).

A recent study (Jayaram-Lindstrom *et al.*, 2008) conducted in Sweden observed that naltrexone, an opioid agonist, in amphetamine-dependent patients significantly attenuated the subjective effects produced by dexamphetamine in those patients. Pre-treatment with naltrexone also significantly blocked the craving for dexamphetamine.

Modafinil, a novel non-amphetamine-type stimulant approved in Australia for the treatment of narcolepsy and sleep apnoea-related fatigue, may be moderately beneficial in reducing methamphetamine use in selected subjects. When compared with placebo in treating methamphetamine dependence in a study conducted by Shearer and colleagues (Shearer *et al.*, 2009), modafinil led to the greatest reductions in methamphetamine use in methamphetamine -dependent subjects who had no other forms of substance dependence. However, no differences were reported between modafinil and placebo in retention, methamphetamine abstinence, methamphetamine craving or severity of dependence.

Dexamphetamine has also been studied in the treatment of methamphetamine dependence. A preliminary study investigating the safety and efficacy of once-daily sustained-release dexamphetamine in people dependent on methamphetamine found that a maintenance pharmacotherapy programme of daily sustained-release amphetamine is both feasible and safe (Longo *et al.*). Compared with placebo,

7 Overall Conclusions and Recommendations

treatment of methamphetamine dependence using sustained-release dexamphetamine was associated with significantly better retention and lower degree of dependence. There was also a general decrease in methamphetamine use and withdrawal symptom severity.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant that causes blockade of inhibitory α_2 -adrenergic autoreceptors on noradrenaline and serotonin neurones, was studied by Cruickshank and colleagues in the management of methamphetamine withdrawal (Cruickshank *et al.*, 2008). Their 2-week study concluded that mirtazapine is not more effective than placebo in improving treatment and retention, or alleviating methamphetamine withdrawal symptoms in an out-patient setting.

Bupropion, a dopamine and norepinephrine reuptake inhibitor that has been approved as an antidepressant and a smoking cessation drug, was also found to be no more effective than placebo in reducing methamphetamine cravings, depressive symptoms, and methamphetamine use in a study conducted by Shoptaw *et al.* (Shoptaw *et al.*, 2008). However, another study (Elkashef *et al.*, 2008) reported that bupropion, when used in combination with behavioural group therapy, was effective for increasing the number of weeks of abstinence in individuals with low-to-moderate methamphetamine dependence.

7 Overall Conclusions and Recommendations

Relapse prevention

Preventing relapse is necessary for maintaining the treatment effects and keeping the patient away from illicit drug use. As with other chronic conditions, episodes of relapse may sometimes require a return to prior treatment components.

In relapse prevention measures, patients are educated to raise awareness on relapse causing factors and high-risk situations, and learn to avoid or cope with those situations. Sometimes pharmacotherapy is used (Bruce, 2000). Antidepressants, for example, are administered when mood is a constant trigger for relapse. Lastly, patients need to make lifestyle changes to steer away from drug misuse to a more normalised and socialised lifestyle (Bruce, 2000).

Aripiprazole in the treatment of methamphetamine dependence

While effective agonist and antagonist pharmacotherapies, as well as symptomatic treatments, exist for opioid dependence, no pharmacological treatment has been found effective and approved for the treatment of methamphetamine abuse or dependence (Grabowski *et al.*, 2004).

A treatment that is able to normalize the altered systems due to methamphetamine abuse could have a beneficial clinical effect on methamphetamine dependence. A 'replacement' strategy paralleling that for opioid dependence that may be effective in treating methamphetamine dependence is the use of partial agonists, which

7 Overall Conclusions and Recommendations

have significant receptor affinity but low intrinsic activity (Childress and O'brien, 2000).

Under conditions of low neurotransmitter tone, as is observed for dopamine during initial abstinence from chronic stimulant administration (Volkow *et al.*, 2001, Weiss *et al.*, 1992), a partial agonist should produce some receptor stimulation, and may therefore function as a replacement medication. A partial agonist may also act as an antagonist when there are higher levels of neurotransmitter present in the synapse, as would occur following use of a stimulant upon relapse.

Due to its unique mechanism of action, partial agonist aripiprazole is hypothesized to be able to restore neurotransmitter balance and the normal function of the mesolimbic dopamine system (Lile *et al.*, 2005), and thus a promising replacement medication for psychostimulant addiction.

The effect of aripiprazole in psychostimulant abuse has been studied in both animals and human beings. In animals, for example, Leite and colleagues showed that aripiprazole inhibited the motor hyperactivity induced by amphetamine and cocaine in mice, but without causing significant motor impairment (Leite *et al.*, 2008).

An interesting study by Schwabe and Koch (Schwabe and Koch, 2007) recently investigated whether aripiprazole could restore animals' responding for reward pellets after amphetamine withdrawal. Withdrawal from repeated amphetamine administration has been

7 Overall Conclusions and Recommendations

shown to decrease the motivation to work for a natural reward in rats, a phenomenon thought to be associated with hypofunction of the mesolimbic dopamine system. Their study showed that low doses of aripiprazole prevented this effect, suggesting that aripiprazole may have potential use as a treatment for the motivational effects of the acute withdrawal stage of ATS addiction cycle.

In humans, aripiprazole has been studied in schizophrenic cocaine-dependent subjects. While traditional antipsychotic medications (i.e. D₂ dopamine receptor antagonist) may leave patients with a shortage of dopamine activity, worsened by receptors that have already been damaged by chronic cocaine use (Zimmet *et al.*, 2000), aripiprazole was able to reduce the actual cocaine use and lessen the desire for cocaine in this patient population (Beresford *et al.*, 2005).

In the context of amphetamine abuse and addiction, aripiprazole has been demonstrated to attenuate many of the behavioral effects of d-amphetamine, including studies by Stoops *et al.* (Stoops *et al.*, 2006, Stoops, 2006) that showed aripiprazole attenuated some abuse-related behavioral effects of d-amphetamine in healthy volunteers.

While Stoops' study (Stoops *et al.*, 2006) result indicated the clinical utility of aripiprazole in the management of ATS abuse and dependence, it should be noted that their experiments used acute aripiprazole administration in combination with d-amphetamine. In a clinical setting, aripiprazole would be administered chronically to methamphetamine abusers. Therefore, further laboratory studies

7 Overall Conclusions and Recommendations

should investigate the ability of chronically administered aripiprazole to attenuate the behavioral effects of methamphetamine.

However, there were two studies that failed to show the effectiveness of aripiprazole in the treatment of methamphetamine dependence.

In the study by Tiihonen and colleagues (Tiihonen *et al.*, 2007), individuals with amphetamine/ methamphetamine dependence were randomly assigned to receive aripiprazole (15 mg/day), slow-release methylphenidate (54 mg/day) or placebo for 20 weeks. The study was terminated prematurely because patients allocated to aripiprazole had significantly more amphetamine-positive urine samples than patients in the placebo group. Aripiprazole was not effective in that trial, but the investigators could not draw any conclusion on its potential efficacy.

Another small 2-week study conducted by Newton *et al.* (Newton *et al.*, 2008) showed similar results. When aripiprazole 15 mg/day was administered to 16 methamphetamine dependent patients, the drug appeared to increase some of the rewarding and stimulatory effects produced by acute methamphetamine, suggesting that 15 mg aripiprazole is unlikely to be efficacious for the treatment of methamphetamine dependence. However, the study group concluded that further research to evaluate the efficacy of lower doses of aripiprazole in relapse prevention should be conducted before ruling out aripiprazole as a treatment for this group of patient population.

7 Overall Conclusions and Recommendations

Methamphetamine dependence and psychosis

Psychosis is a known complication of methamphetamine abuse and dependence. While transient psychotic symptoms may occur during intoxication with methamphetamine use, it is possible that psychotic symptoms will persist (Van Kampen and Katz, 2001). When the psychotic symptoms persist and interfere with the patient's social and occupational functioning, treatment should be targeted to psychiatric symptoms present (Larson, 2008).

Aripiprazole, the sixth atypical antipsychotic medication, was first approved by the Food and Drug Administration (FDA) in 2002 for the treatment of schizophrenia. Available as tablets for oral administration, aripiprazole is also indicated for the treatment of acute manic episodes associated with bipolar 1 disorder since 2004. This makes aripiprazole a good candidate for the treatment of methamphetamine dependence who presented with psychotic symptoms.

7 Overall Conclusions and Recommendations

6.3 Systematic review on the aripiprazole as treatment of amphetamine and methamphetamine dependence patients

6.3.1. Methods

6.3.2. Search strategy

This systematic review included literature published between January 2000 and April 2011. An electronic search on the following databases was carried out: PUBMED, Web of Science, OVID Medline (R), the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Review, using the search terms:

Systematic review 1

- (d) Methamphetamine or Methamfetamine
- (e) Aripiprazole
- (f) Drug dependence

Systematic review 2

- (d) Amphetamine
- (e) Aripiprazole
- (f) Drug dependence

Where Medical Subject Headings (MeSH) terms were available, they were exploded and combined. Reference lists from retrieved papers were also searched.

7 Overall Conclusions and Recommendations

6.3.3. Type of studies

Only publication in English for experimental studies (e.g. randomized clinical trials) and systematic review were included if:

- (a) Participants were treated with aripiprazole
- (b) Methamphetamine or amphetamine dependence

6.3.4. Types of participant

Male or female patients, of any age or ethnic origin, who has methamphetamine or amphetamine dependence.

6.3.5. Types of interventions

The treatment group was aripiprazole and the comparison groups were either any antipsychotic drugs or placebo or non-drug treatment.

6.3.6. Types of outcome measures

The changes in craving, the retention rate of the study or treatment response rate.

6.3.7. Data extraction

Information was extracted on data source such as participants, interventions, results and outcome.

6.3.8. Results

A total of 5 experimental studies for methamphetamine dependence and 12 experimental studies for amphetamine dependence were identified by the search and cross-referencing strategies.

7 Overall Conclusions and Recommendations

Figure 6.1 Flow chart showing the article-identification process for methamphetamine dependent

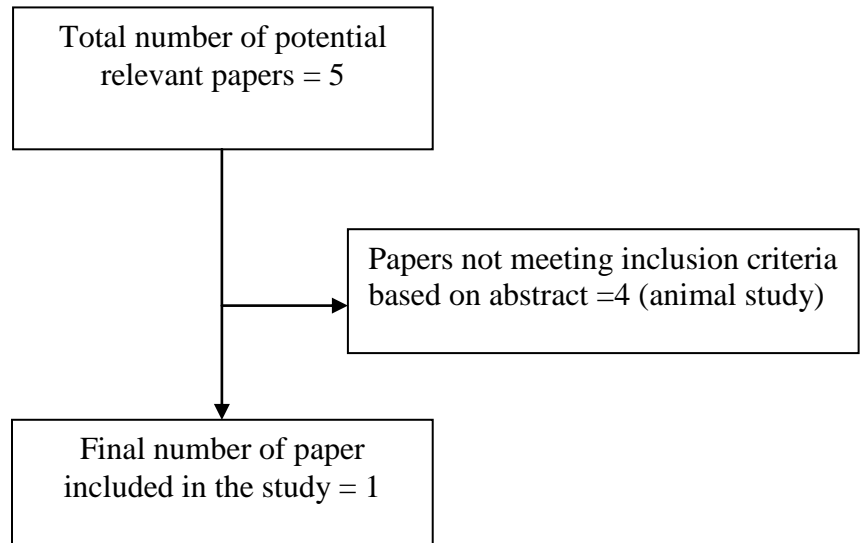
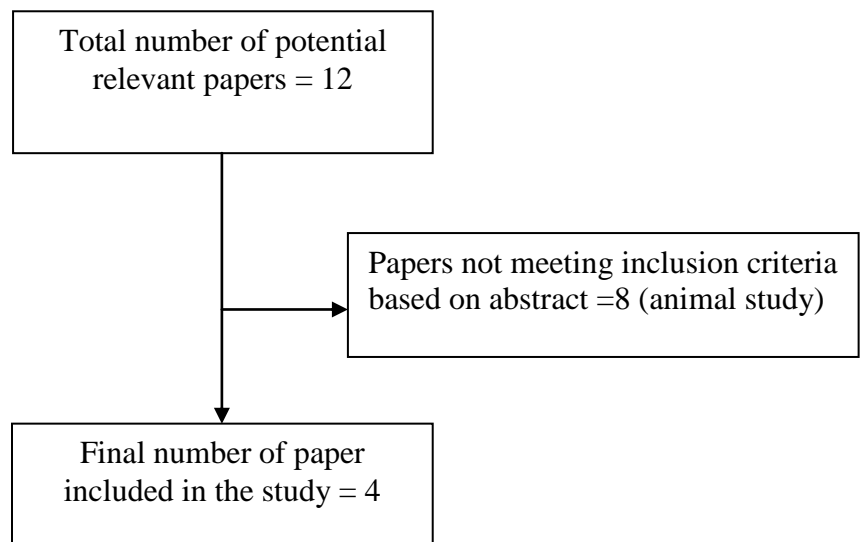


Figure 6.2 Flow chart showing the article-identification process for amphetamine dependent



7 Overall Conclusions and Recommendations

Table 6.1 Systematic review on the aripiprazole as treatment of methamphetamine dependence patients					
Study	Study Subjects	Intervention	Outcome	Results	Comments
(Newton <i>et al.</i> , 2008)	Methamphetamine dependence 16 participants	i) intravenous methamphetamine 15mg then randomized to oral aripiprazole 15mg or placebo 2 days later ii) intravenous methamphetamine 30mg then randomized to oral aripiprazole 15mg or placebo	Abstinence related craving	Aripiprazole associated with increased craving independent of methamphetamine dosing.	Suggested experimental study with lower dose of aripiprazole

7 Overall Conclusions and Recommendations

Table 6.2 Systematic review on the aripiprazole as treatment of amphetamine dependence patients					
Study	Study Subjects	Intervention	Outcome	Results	Comments
(Tiihonen <i>et al.</i> , 2007)	DSM-IV criteria for amphetamine dependence 53 participants	3 arms i) oral aripiprazole 15mg/day ii) slow-release methylphenidate 54mg/day iii) placebo For 20 weeks	proportion of amphetamine-positive urine samples	Aripiprazole had significantly more amphetamine-positive urine samples than patients in placebo group, the patients allocated with methylphenidate had fewer positive urine sample than patients receiving placebo	This study was stop due to safety issue during interim analysis(actual sample size 210 subjects)
(Lile <i>et al.</i> , 2005)	7 healthy subjects with a lifetime history of nontherapeutic use of a stimulant	i) To discriminate between 15 mg oral D-amphetamine or placebo later ii) to assess the effects of a range of doses of D-amphetamine (0,2.5,5,10 and 15 mg)alone and in combination with aripiprazole(0 and 20 mg)	Rating scale of active, alert and energetic, blood pressure and heart rate.	Aripiprazole significantly attenuated the discriminative-stimulus and cardiovascular effects of D-amphetamine.	The preclinical findings can be used to investigate the ability of aripiprazole for other stimulants dependence.
(Stoops, 2006)	Healthy subjects with a lifetime history of nontherapeutic use of a stimulant Experiment 1 has 7 subjects Experiment 2 has 6 subjects	To discriminate between 15 mg oral D-amphetamine or placebo later Experimental 1: to assess the effects of a range of doses of D-amphetamine (0,2.5,5,10 and 15 mg)alone and in combination with aripiprazole(0 and 20 mg) Experimental 2: to assess the effects of a range of doses of D-amphetamine (0,2.5,5,10 and 15 mg)alone and in combination with aripiprazole(0 and 10 mg)	Rating scale of active, alert and energetic.	Experimental 1: higher dose of Aripiprazole significantly attenuated the discriminative-stimulus Experimental 2: lower dose of Aripiprazole significantly attenuated the discriminative-stimulus	The findings of experimental 1 is similar with Lile <i>et al.</i> , 2005)

7 Overall Conclusions and Recommendations

Table 6.2 Systematic review on the aripiprazole as treatment of amphetamine dependence patients(con't)					
Study	Study Subjects	Intervention	Outcome	Results	Comments
(Stoops <i>et al.</i> , 2006)	6 healthy subjects with a lifetime history of nontherapeutic use of a stimulant	i)To discriminate between 15 mg oral D-amphetamine or placebo later ii)to assess the effects of a range of doses of D-amphetamine (0,2.5,5,10 and 15 mg)alone and in combination with aripiprazole(0 and 10 mg)	Rating scale of active, alert and energetic, blood pressure and heart rate.	Aripiprazole significantly attenuated the discriminative-stimulus and cardiovascular effects of D-amphetamine.	The findings of this study similar with experimental 2 in Stoops study.(Stoops, 2006) 10 mg of aripiprazole would be reasonable starting dose for the treatment of stimulant abuse and dependence.

7 Overall Conclusions and Recommendations

6.3.9. RESEARCH QUESTION

Is aripiprazole has better safety and efficacy compare to placebo in methamphetamine dependence patients?

6.3.10. STUDY OBJECTIVES

Primary Objective

To determine the efficacy of Aripiprazole in maintaining of abstinence and retention among methamphetamine dependence patients.

Secondary objective

To determine the safety of Aripiprazole in the treatment of methamphetamine dependence patients.

Tertiary objective

- i). To determine whether Aripiprazole treatment will reduce methamphetamine withdrawal symptoms.
- ii). To determine the efficacy of Aripiprazole in reducing anxiety and depressive symptoms among methamphetamine dependence patients.
- iii). To determine the efficacy of Aripiprazole in preventing psychotic symptoms among methamphetamine dependence patients.

7 Overall Conclusions and Recommendations

6.3.11. HYPOTHESES

Hypothesis for primary objective:

- i). The aripiprazole-treated subjects have lower proportion of positive urine samples than subjects given placebo between baseline, day 7, day 14, day 28, day 42 and day 56.
- ii). The proportion of retention for subjects treated with aripiprazole was higher compare to placebo-treated subjects.
- iii). The mean duration of follow-up among aripiprazole-treated subjects was longer than compare placebo-treated subjects.

Hypothesis for secondary objective:

- i). There was no difference in the proportions of adverse events between aripiprazole-treated and placebo-treated subjects.
- ii). Aripiprazole-treated subjects will not show a significantly increase in BAS, SAS, AIMS scores between baseline, day 14 and day 42.

Hypothesis for tertiary objective:

- i). Aripiprazole-treated subjects have a significantly greater reduction in PANSS means scores than subjects given placebo between baseline, day 14 and day 56.
- ii). Aripiprazole-treated subjects have a significantly greater reduction in CGI means scores than subjects given placebo between baseline, day 14 and day 56.

7 Overall Conclusions and Recommendations

- iii). Aripiprazole-treated subjects have a significantly greater reduction in HADS-anxiety means scores than subjects given placebo between baseline, day 14 and day 42.
- iv). Aripiprazole-treated subjects have a significantly greater reduction in HADS-depression means scores than subjects given placebo between baseline, day 14 and day 42.
- v). Aripiprazole-treated subjects have a significantly greater reduction in Brief Substance Craving Scale (BSCS) means scores than subjects given placebo between baseline, day 7, day 14, day 28, day 42 and day 56.

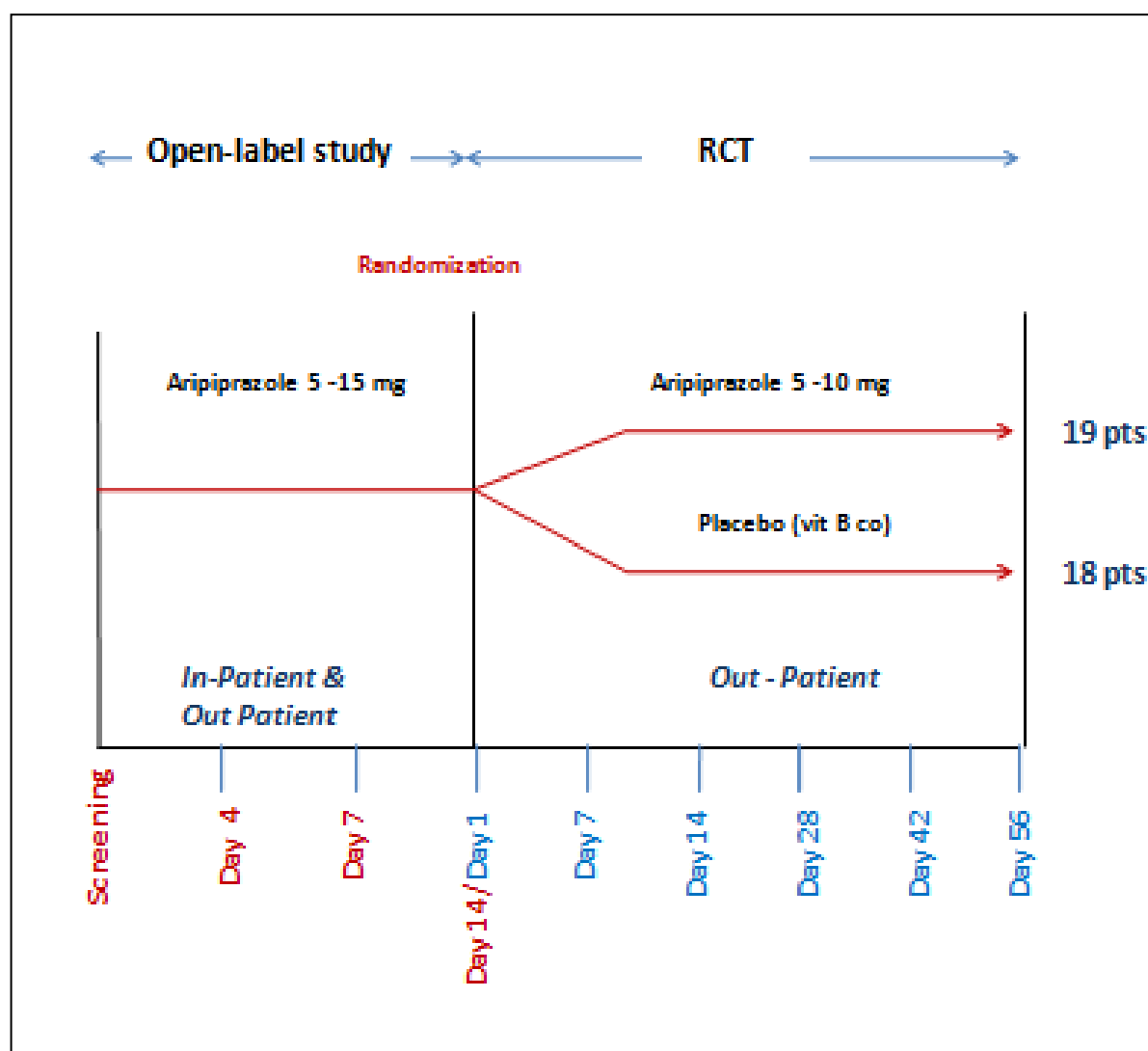
7 Overall Conclusions and Recommendations

6.4 Methodology

6.4.1. Study Design

This study was a randomized double-blind placebo-controlled parallel trial. This study was the continuity from the open-label study in chapter 5.

Figure 6.3 The overall study design for methamphetamine-induced psychosis and methamphetamine dependence study



6.4.2. Study Period

The study period was from July 2007 until June 2011. Data was collected from September 2008 to December 2010.

7 Overall Conclusions and Recommendations

6.4.3. Location of Study

This study was conducted at the outpatient psychiatric clinic in University Malaya Medical Centre (UMMC).

6.4.4. Study Population

The study population included male or female with current DSM-IV diagnoses of methamphetamine dependence.

6.4.5. Inclusion Criteria

- i). Male or female, aged 18 – 60 years.
- ii). Primary diagnosis of methamphetamine dependence confirmed by DSM-IV. Patient must not have current dependence with other substances such as alcohol, cocaine, opiates and marijuana except for nicotine. However, abuse of these drugs was allowed for this study.
- iii). Urine positive for methamphetamine and within 30 days of last use of the methamphetamine.
- iv). Must have been using methamphetamine at least once a week for the past three months at enrollment.
- v). History of having psychotic symptom prior to randomization.
- vi). History of treatment with aripiprazole at least 2 weeks prior to randomization.

7 Overall Conclusions and Recommendations

- vii). Present without any current intoxication effects of methamphetamine to provide written consent at the time of the baseline session and to comply with study procedures.
- viii). No diagnosis of schizophrenia, schizoaffective disorder, bipolar affective disorder, major depression with psychotic symptoms, delusional disorder, organic brain disease, dementia, or any diseases that require other antipsychotics. If they have a history of a mood and anxiety disorder, they were not on pharmacological treatment for at least the previous two weeks.
- ix). Patient was not currently taking psychotropics such as antipsychotic except for aripiprazole, mood stabilizer, anti-anxiety or antidepressant medications.
- x). Using a barrier (diaphragm or condom) with spermicide, intrauterine device (IUD), or complete abstinence as a method of birth control (if a woman of child-bearing capacity).
- xi). Patient was not suicidal or homicidal.

6.4.6. Exclusion Criteria

- i). Serious medical illnesses that potentially progress to life-threatening medical illness which may compromise patient safety or study conduct.
- ii). Known hypersensitivity or allergy to Aripiprazole.

7 Overall Conclusions and Recommendations

- iii). Documented history of schizophrenia, bipolar, organic brain disease, dementia, or any diseases that require other antipsychotics.
- iv). Clinically significant abnormal laboratory values.
- v). Female who is positive on a urine pregnancy test or lactating.

6.4.7. Sample size estimation

Based on previous studies (Tiihonen *et al.*, 2007, Newton *et al.*, 2008), the minimum sample size required for this study was calculated by using the PS software.

- i). The power of the study is taken at 80% level.
- ii). The significance level of the statistic tests done was at 95% Confidence Interval level and α was set at 0.05. The Null hypothesis was rejected when $p < 0.05$.
- iii). p_0 - The probability of the outcome for the control patient (failure in maintaining retention) is 0.95.
- iv). p_1 - The probability of the outcome for the intervention patient (failure in maintaining retention) is 0.5.
- v). The ratio of case to control is taken as 1 : 1.

Therefore the sample size obtained for this study as follow:

Number of treatment arm	=	18 patients
Number of control arm	=	18 patients
Total number of subjects	=	36 patients

7 Overall Conclusions and Recommendations

6.4.8. Study Variables

The study variables that were considered for analysis in this study population were as follows:

(Operational definitions in ANNEX A)

6.4.8.1 Primary Study Endpoints

- Urine toxicology screened for methamphetamine.

Urine samples were collected during visit day 7, 14, 28, 42 and day 56.

- The proportion of outpatient attending research evaluation visits for aripiprazole and placebo.

Patients were scheduled for research evaluation visits on day 7, 14, 28, 42 and day 56.

6.4.8.2 Secondary Study Endpoint

- The means scores of BAS, SAS, AIMS rating scale to measure the safety of aripiprazole
- To describe all side effects reported by patients during the study.

Patients were assessed on 14 day 42.

6.4.8.4 Tertiary Study Endpoint

- The means score of Brief Substance Craving Scale (BSCS)

Patients were assessed on day 7, 14, 28, 42 and day 56.

7 Overall Conclusions and Recommendations

- The means score of HADS-anxiety and HADS-depression rating scale

Patients were assessed on 14 day 42.

- The means score of PANSS and CGI.

Patients were assessed on 14 day 56.

6.4.8.4 Descriptive Variables

Sociodemographic Variables

- i). Age
- ii). Sex
- iii). Race
- iv). Employment pattern (For the past 2 years)
- v). Total family income
- vi). Educational level
- vii). Marital status
- viii). Number of siblings

Drug dependence and abuse history

- i). Duration of methamphetamine used
- ii). Age of first methamphetamine used
- iii). Amount of money spend monthly for methamphetamine
- iv). Route of methamphetamine

7 Overall Conclusions and Recommendations

- v). History of nicotine dependence
- vi). History of alcohol abuse
- vii). History of other drug used

6.4.9. Study Instruments

Major Axis I psychiatric disorder assessment

**i). MINI International Neuropsychiatric Interview (M.I.N.I.)
(Sheehan *et al.*, 1998b)**

This was a face-to-face structured interview for the Major Axis I psychiatric disorder in DSM-IV and ICD-10. The M.I.N.I. is a short structured diagnostic interview for DSM-IV or ICD-10 psychiatric disorders for the Major Axis I psychiatric disorder including suicidality. It has been widely used in international clinical trials and epidemiological studies (Joling *et al.*, 2008, Van't Veer-Tazelaar *et al.*, 2009). The MINI was available in local language (Sheehan *et al.*, 1998a).

ii). Brief Substance Craving Scale (BSCA) (Somoza E, 1999b)

The BSCS uses Likert scales, ranging from 0 to 4, to assess methamphetamine craving on 3 dimensions of craving: intensity, length, and frequency. A composite score is derived from the total of these items.

7 Overall Conclusions and Recommendations

iii). Positive and Negative Symptoms Scale (PANSS) (Kay *et al.*, 1987)

The Positive and Negative Syndrome Scale (PANSS) is a medical scale used for measuring symptom severity of patients with schizophrenia. It refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association: positive symptoms, which refer to an excess or distortion of normal functions (e.g. hallucinations and delusions), and negative symptoms, which represent a diminution or loss of normal functions. A face-to-face interview of the scale will capture three components: positive scale (7 items), negative scale (7 items) and general psychopathology scale (16 items).

iv). Abnormal Involuntary Movement Scale (AIMS) (Rush, 2000)

The Abnormal Involuntary Movement Scale (AIMS) is a rating scale that was originally designed in Italian language in the 1980s, (Burti *et al.*, 1981) to measure involuntary movements known as tardive dyskinesia (TD). TD is a disorder that sometimes develops as a side effect of long-term treatment with neuroleptic (antipsychotic) medications. The AIMS test is used not only to detect tardive dyskinesia but also to follow the severity of a patient's TD over time. It is a valuable tool for clinicians who are monitoring the effects of long-term treatment with neuroleptic medications and also for researchers studying the effects of these drugs. The AIMS test was originally developed for administration by trained clinicians.

7 Overall Conclusions and Recommendations

v). Barnes Akathisia Scale (BAS) (Barnes, 1989)

The Barnes Akathisia Scale (commonly known as BAS or BARS) is a rating scale that is administered by physicians to assess the severity of drug-induced akathisia. The Barnes Akathisia Scale is the most widely used rating scale for akathisia. This scale includes objective and subjective items such as the level of the patient's restlessness. It comprises items for rating the observable, restless movements which characterise the condition, the subjective awareness of restlessness, and any distress associated with the akathisia. In addition, there is an item for rating global severity. A standard examination procedure is recommended. The inter-rater reliability for the scale items (Cohen's kappa) ranged from 0.738 to 0.955.

Akathisia is a syndrome of motor restlessness, principally seen in association with antipsychotic medication. It is characterized by a subjective experience of mental unease and the urge to move, and manifests physically as particular patterns of restless movement.

vi). Simpson Angus Scale (SAS) (Simpson and Angus, 1970)

Simpson-Angus Scale (SAS) is a 10-item rating scale that has been used widely for assessment of Neuroleptic-Induced Parkinson in both clinical practice and research settings. It consists of one item measuring gait (hypokinesia), six items measuring rigidity and three items measuring glabella tap, tremor and salivation, respectively. Items

7 Overall Conclusions and Recommendations

are rated for severity on a 0-4 scale, with definitions given for each anchor point. It is an established rating scale. SAS is a reliable and a valid instrument. It performs well and similarly to DSM-IV in Neuroleptic Induce Parkinsonism case detection (Janno *et al.*, 2005).

vii). Clinical Global Impression Scale (CGI)

The Clinical Global Impression rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders (Guy, 1976). Many researchers, while recognizing the validity of the scale, consider it to be subjective as it requires the user of the scale to compare the subjects to typical patients in the clinician experience (Haro *et al.*, 2003, Huber *et al.*, 2008).

The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1=normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

viii). Hospital Anxiety Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) was developed by Zigmond and Snaith (Zigmond and Snaith, 1983) in 1983. Its purpose

7 Overall Conclusions and Recommendations

is to provide clinicians with an acceptable, reliable, valid and easy to use practical tool for identifying and quantifying depression and anxiety. The role of the scale is dimensional rather than categorical; it is best used not to make diagnoses of psychiatric disorders, but for identifying general hospital patients who need further psychiatric evaluation and assistance (Herrmann, 1997).

The HADS is a self-report rating scale of 14 items on a 4-point Likert scale (range 0–3). It is designed to measure anxiety and depression (7 items for each subscale). The total score is the sum of the 14 items, and for each subscale the score is the sum of the respective seven items (ranging from 0–21). It is worth noting that items referring to depression symptoms that describe somatic aspects of depression (e.g. insomnia and weight loss) are not included in the scale.

The HADS has been translated and widely used in more than 25 countries since its original development. Herrmann, in an extended review, reported that the HADS has demonstrated reliability and validity when used to assess medical patients (Herrmann, 1997). Bjelland reached similar conclusions in his review 5 years later (Bjelland *et al.*, 2002). The HADS has been used in the general population (Mykletun *et al.*, 2001), on general hospital patients (Johnston *et al.*, 2000), in cancer care settings (Moorey *et al.*, 1991), and even in HIV patients (Savard *et al.*, 1998).

ix). Structured Questionnaires

7 Overall Conclusions and Recommendations

The patients were screened in order to identify methamphetamine dependence by using a structured questionnaire, which consists of four sections. The first section was to assess the demographic data of the study population. The second section was to identify the characteristics of crimes/illegal activities. The third section was to obtain the medical history and the last section was to assess the social and emotional factors among the patients.

6.4.10. Study Drug

6.4.10.1 Intervention

Aripiprazole is a psychotropic drug. It is a light yellow colour, round, flat, bevelled edged, uncoated tablets that contain 10mg of aripiprazole. Aripiprazole was put in an opaque gelatine capsule in order to be identical to the placebo.

6.4.10.2 Placebo

The placebo formulation for this study is vitamin B complex in a tablet form. In order for the placebo to appear identical to aripiprazole, the placebo was put in an opaque gelatine capsule that has same colour, shape and size for aripiprazole.

6.4.10.3 Concomitant Therapy

The concomitant medications such as benzodiazepine and benzhexol were allowed for this study.

Commitment therapy that not permitted during the study was:

7 Overall Conclusions and Recommendations

- i). Carbamazepine
- ii). Ketoconazole
- iii). Quinidine
- iv). Fluoxetine
- v). Paroxetine

6.4.10.4 Packaging of Study Drug

Study drug (intervention) was supplied in bulk shipments by a pharmaceutical company whereas placebo (vitamin B complex) was obtained from a pharmacy. A study coordinator repackaged the bulk drug into packs containing seven gelatin capsules per pack (10mg each for aripiprazole).

A separate pack containing seven capsules per pack with 5 mg each for aripiprazole was done, in case patient could not tolerate the 10 mg of aripiprazole.

6.4.10.5 Receiving, Storage, Dispensing and Return

i). Receipt of Drug Supplies

An inventory was performed after accepting the drug shipment. The study coordinator counted and verified the shipment containing all the items mentioned in the supply. The investigator would notify to the pharmaceutical company of any damage of the study drug.

7 Overall Conclusions and Recommendations

ii). Storage

Stock study drug and drug packaged in patient kits were stored in a locked cabinet in the research centre with climate control maintaining the temperatures within a range of 20°C to 25°C. Only the study coordinator and principal investigator have access to the study drug.

iii). Dispensing of Study Drug

The principal investigator or study coordinator would dispense the appropriate amount of study drug, according to the number of days of follow up of the research subject based on the randomization list. Subject compliance monitoring was conducted by doing pill counts at every study visit for all patients.

iv). Return of Study Drug

At the completion of the study, the final reconciliation of drug shipped, drug consumed and drug remaining was done. After appropriate accounting the pharmaceutical company was informed, the unused study drug was returned to the pharmaceutical company.

6.4.11. Conduct of study

i). Training of study coordinator

The study coordinator was trained with regards to the screening, recruitment and interviewing the study patient for the baseline

7 Overall Conclusions and Recommendations

characteristics. She was also trained about the procedure in handling the study drug.

ii). Pre-test

A pre-test of the structured questionnaires was done on 10 patients who were attending the substances dependence clinic at UMMC. Some corrections were made to facilitate patients' understanding of the questionnaires.

iii). Subject recruitment and screening

All patients from the previous open label study (chapter 5) were approached during this study. Some of the patients were recruited from the response of this study newspaper advertisement, as well as articles written up by principal investigator in newspaper pertaining to methamphetamine dependence. Patients were briefed on this study and written consent was obtained. Prior to the consent, patient was explained detailed information about aripiprazole, the rationale for why it was being studied, frequency of dosing, and length of treatment, potential benefits, side effects and risks, safeguards and emergency procedures. The collections of all laboratory specimens were described in detail, as the number and frequency of the research interviews and self-assessments. Patients were assured that their participation was voluntary and that withdrawal from the study would not jeopardize current or future treatment. Randomization was explained to the patients, as they would know their treatment assignment at the end of the study, after the blind has broken.

7 Overall Conclusions and Recommendations

A M.I.N.I was administered to obtain DSM-IV diagnoses of methamphetamine dependence and to rule out other psychiatric disorders. All medications taken by the patient for the 30 days prior to screening was documented. A face-to-face interview was conducted to collect primary data by using a structured questionnaire. Some secondary data pertaining to patient and family medical history were obtained from patient's case note. Only patients who were methamphetamine positive during urine screening of open-label study were included in this study. The principal investigator confirmed and signed off on the inclusion and exclusion criteria on a case report form (CRF) prior to the patient formally recruited in the study or given study medication.

iv). Baseline visit

The patients were further assessed with M.I.N.I. for the Major Axis I psychiatric disorder and evaluated BSCA, PANSS, AIMS, BAS, SAS, CGI and HADS. A complete physical examination was done including vital signs and weight. A urine pregnancy test was conducted for female patients with childbearing capability.

v). Randomization

Patients were assigned to the study drugs according to a randomization list. The randomization list in the block of 4 was computer generated by Randomization.com programme. Patients were randomized to one of two treatment of either aripiprazole 10mg/day (n = 19) or placebo (n = 18). Randomization code for aripiprazole and

7 Overall Conclusions and Recommendations

placebo, either A or B was done by an independent person. The randomization code was put in an envelope and kept in the Psychiatric Unit Research Center, PPUM. It was only can be assessed by principle investigator in the case of severe adverse event happen during the study.

vi).Blinding of Study Drug

Seems this was a double blind study, both patients and the assessor were blinded to the study drug.

vii). Method for assigning subjects to treatment groups

Patients were randomized according to the following regimen:

Study drug (Aripiprazole-10mg each or placebo): one tablet orally, administered as a single dose, for 56 days (8 weeks). Patients would take the study drug daily dose at 8:00 a.m.

viii). Follow-Up Evaluation

A follow-up evaluation was scheduled on day 7,14, 28, 42 day 56 after the beginning of the study. If subjects could not attend the scheduled visit, subject was given appointment on the subsequent day.

At each follow-up evaluation, urine sample was collected from patients and urine toxicology was performed for methamphetamine. Their vital signs and weights were measured, and any adverse event was recorded. Patients were evaluated BSCA, PANSS, AIMS, BAS, SAS, CGI and HADS.

7 Overall Conclusions and Recommendations

If subjects experienced significant side effects from the study drug (Aripiprazole or placebo), the principal investigator would have the option to reduce the dose for aripiprazole or vitamin B Complex during the study, depending on the clinical interview. Acceptable dose reduction for aripiprazole was from one tablet per day (10 mg/day) to half tablets per day 5 mg/day, and for patients receiving placebo, vitamin B complex aripiprazole from one tablet per day was reduced to half tablet per day. Upward titration following a dose reduction was allowed during the trial. Dose titration was documented in the study chart along with the clinical rationale. At the end of the study drug treatment period, study drug was discontinued without tapering.

The concomitant medications were reviewed. Finally pill count was done, the unused study drug was collected from the previous follow up and dispensed the new study drug. During the study visit, the study termination form was completed in case of discontinuation of patient from this study.

ix). Subject Compliance Monitoring

The research coordinator conducted pill counts at the follow-up visit of all study patients. Unused amounts were documented. Proper drug dosing was reviewed with patients at each visit with clear instructions to take all study drugs as directed.

x). End of medication evaluation

This evaluation was scheduled on the day 56 study drug treatment period. At this meeting, the following evaluations were completed:

7 Overall Conclusions and Recommendations

- | | |
|---------------------------|---------|
| 1) Physical examination | 6) BARS |
| 2) Vital signs and weight | 7) SAS |
| 3) PANSS | 8) AIMS |
| 4) CGI-S | 9) BSCS |
| 5) HADS | |

xi). Early withdrawal of subjects

Any patients experiencing a serious adverse event felt to be related to study drug were withdrawn from the study. Patients were also withdrawn if they required hospitalization for addiction or psychiatric treatment, received other psychotropic medications, or if discontinuation from the study was deemed by the principal investigator based on their best interest. Any patient withdrawing their consent to participate in the study or their authorization to use their protected health information was withdrawn from the study. Patients discontinued from the clinical trial were given appropriate treatment referrals to the outpatient psychiatric clinic, UMMC. Patients were instructed to return all unused medications. For the early withdrawal, patients had all final assessments that originally were scheduled for the end of study visit.

All patients randomized into the study were included in the final study analyses. Patients were not dropped from all study activities unless they requested not to be contacted or could not be located for the 2-weeks follow-up assessment. Patients were informed at the consent session that treatment might be discontinued due to:

7 Overall Conclusions and Recommendations

- Intolerable side effects
- Development or exacerbation of psychiatric symptoms necessitating inpatient admission or a more aggressive therapeutic intervention than was provided by the protocol
- Methamphetamine or other substance abuse necessitating inpatient admission or a more aggressive treatment than was provided by the protocol
- Clinical deterioration for any reason or any clinical status that necessitates inpatient admission
- Incarceration for more than 2 weeks
- Failure to attend 3 consecutive outpatient evaluation visits
- Failure to provide laboratory specimens

Reasons why patients discontinued from the clinical trial were documented on the Study Termination Form, along with any referrals that were made. A final safety evaluation was conducted as soon as possible on all randomized patients who have been discontinued from the study.

6.4.12. Safety and Adverse Events

i). Recording of Adverse Events

During the research evaluation visit, the patient was asked on adverse events through specific questioning and by examination. Information on all adverse events was recorded immediately in the case report form

7 Overall Conclusions and Recommendations

(CRF). Each adverse event was followed up until resolution or stabilization has been achieved.

In the case of the occurrence of serious adverse event (SAE), it was followed up to determine the final outcome. Any serious adverse event that occurred after the study period was considered possibly related to the study drug, was recorded and reported immediately.

ii). Reporting of Serious Adverse Events To Ethic Committee (EC) by Principal Investigator

A serious adverse event must be reported to the EC within 24 hours (one working day) of the event. The principal investigator would keep a copy of the SAE form in the file. Within the following 48 hours, the principal investigator would provide further information and progress on the serious adverse event to the EC.

In the SAE form, the following information should be provided:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event was classified as serious

7 Overall Conclusions and Recommendations

- Principle investigator assessment of the association between the event and study drug

iii). Unblinding Procedures

In the event that patients were prematurely discontinued from the trial, it was necessary to avoid breaking the blind whenever possible, in order to protect the integrity of the study. If an emergency necessitates that the blind be broken, only the principal investigator has the authority to inform the actual study drug to the relevant party.

iv). Medical Monitoring

The principal investigator was responsible to oversee the safety of the study. This safety monitoring would include careful assessment and appropriate reporting of adverse events. Medical monitoring would include a regular assessment of the number and type of serious adverse events.

v). Protection of Subjects

Additional procedures would be conducted to protect the safety of the study patients. Potential patients would be screened for medical illnesses that would preclude the use of aripiprazole. Patients selected for the study would be evaluated weekly for AE while receiving study drug. Venipuncture was carried out with good aseptic technique by an experienced nurse or physician. Before randomized medications, a physical examination, ECG and a urine pregnancy test (if female of childbearing capability) were performed. Patients were given a 24-hour

7 Overall Conclusions and Recommendations

emergency number form them to call if necessary. The principal investigator would follow all patients who were discontinued due to any serious AEs until the AE resolved and become completely stable, unless a referral to another physician or specialist was clinically indicated or requested by the patient.

6.4.13. Data Handling and Record Keeping

i). Data Management

The data were checked before ending each interview session and before compilation to ensure completeness. If missing data was found, the patient will be contacted through telephone. Raw data obtained were coded and entered into Statistical Package for Social Sciences (SPSS) Version 16.0. Statistical analysis was done on an intention-to-treat basis. The primary outcome measure was the proportion of methamphetamine-positive urine samples during the pharmacological treatment. In terms of missing data, they require that the data be missing at random. This means that the missing data contains no information about treatment outcome, beyond that already contained in the observed data.

The data were summarized by running frequency distributions and simple descriptive statistics (means and standard deviations). Cleaning for double entry and outliers before analysis was done.

7 Overall Conclusions and Recommendations

ii). Confidentiality

Information about study patients was kept confidential and managed according to the requirements of the EC.

iii). Source Data and Case Report Form

Source data was all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data were contained in source documents such as hospital records, clinic charts, laboratory results, pharmacy dispensing records, recorded data from automated instruments, microfilm or magnetic media, x-rays, subject files, records kept at the pharmacy, at the laboratories, at medical record department and other related documents.

The study case report form (CRF) was the primary data collection instrument for the study. All data requested on the CRF were recorded and all missing data were explained. "N/D" was written if a space on the CRF was left blank because the procedure was not done or the question was not asked. "N/A" was written if the item was not applicable to the individual case. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line was drawn through the incorrect entry and the correct data was entered above it. All such changes were initialed and dated.

7 Overall Conclusions and Recommendations

6.4.14. Ethical consideration

Ethical clearance had been obtained earlier from UMMC's ethical committee (ANNEX D). The interviewer was required to introduce herself to the subject. Before any interview, patients had been informed regarding the nature and purpose of study and ensuring the respondent on confidentiality of the information. Written consent was obtained from the patients.

6.4.15. Statistical Analysis

i). Univariate analyses

Descriptive statistics were used to summarize demographic variables, history of drug use and adverse events. For nominal independent variables, they were described in the form of frequencies and percentages. For continuous independent variables, they were summarized and described as means, standard deviations and median.

ii). Bivariate analysis

The independent *t*-test was used to examine changes in means of continuous variables and rating scales such as PANSS ,CGI, BSCS, BARS, SAS and AIMS. Skewed data was analysed using non parametric test. The retention in treatment was analysed using Kaplan Meier survivor function. An alpha level of significance 0.05 was set for all analyses.

7 Overall Conclusions and Recommendations

iii). Multivariate Analysis

Categorical repeated measures variables such as primary study hypotheses concerning the effect of aripiprazole versus placebo on urine methamphetamine screen results were examined using generalized estimating equations(GEE). GEE assumes that missing data are missing 'completely at random'. Effect of treatment condition on continuous repeated measures such as PANSS, CGI, HADS and BSCS were evaluated using mixed model approach. Mixed-model repeated measures (MMRM) were employed because it produces unbiased results to the missing data. Drug condition, time and the interaction between drug and time were fitted as main effects for GEE and MMRM.

7 Overall Conclusions and Recommendations

6.5 Results

A total of 145 treatment seeking methamphetamine dependence patients were screened. Seventy-three were eligible for the study but 24 patients declined participations. Forty-nine patients provided informed consent and were treated for two weeks with aripiprazole (open label study in chapter 5). After 2 weeks of aripiprazole treatment, 37 patients fulfil all inclusion criteria and do not have any exclusion criteria. 19 patients were randomized to aripiprazole and 18 to placebo (Figure 6.4). 84.2% of participants randomized to aripiprazole completed the 8 weeks study visit compared to only 50% of participants randomized to placebo ($p < 0.05$).

Baseline Characteristics

The baseline characteristics of participants randomized to aripiprazole and placebo are shown on table 6.3, while the drug history characteristics were shown on table 6.4. There were no significant difference between the aripiprazole and placebo in terms of baseline demographic characteristics and previous drug history.

Retention

The maximum length of time in treatment was 56 days. There was a statistically significant difference between groups in the amount of time spent in treatment ($p < 0.05$), with those given aripiprazole retained for an average of 48.7 days (± 4.0) compared with only 37.1 days (± 5.0) for the placebo group. Time to dropout was also compared between

7 Overall Conclusions and Recommendations

groups (Figure 6.6). The survival curves results showed that participants in the aripiprazole group were less likely to drop out of the study than those in the placebo group. The difference was statistically significant, according to Cox's regression analysis ($p < 0.05$).

Urinalysis Results

There were no statistically significant differences between participants receiving aripiprazole and those receiving placebo in the GEE analysis of urine drug screen results (Figure 6.5, Table 6.5 and Table 6.6).

Psychotic Symptoms

Psychotic symptoms as measured by PANSS decreased among participants who were randomized to aripiprazole treatment but those who were randomized to placebo showed an increased in the total PANSS score (Table 6.12). There was significant effect of the treatment over time in PANSS score during the treatment period between participants in the two treatment conditions using a mixed model repeated measures (MMRM) (Table 6.13).

Similarly the CGI score decreased among participants who were randomized to aripiprazole treatment but those who were randomized to placebo showed an increased in the CGI score (Table 6.12). There was significant effect of the treatment over time in CGI score during the treatment period between participants in the two treatment conditions using MMRM (Table 6.13).

7 Overall Conclusions and Recommendations

Anxiety Symptoms

Anxiety symptoms as measured by HADS decreased among participants who were randomised to aripiprazole treatment but those who were randomised to placebo showed an increased in the HADS score (Table 6.14). There was significant effect of the treatment over time in HADS score during the treatment period between participants in the two treatment conditions using MMRM (Table 6.15).

Depressive Symptoms

Depressive symptoms were measured by using HADS scale. Depressive symptoms were generally lower in aripiprazole treatment arm than in the placebo arm, but the difference was not statistically significant except on Day 14 ($p=0.02$) (Table 6.14). The HADS-depression score in patients receiving aripiprazole decreased from 2.5 ± 23.6 on day 1 to 1.7 ± 2.8 on day 14, but increased to 2.1 ± 2.8 by day 42. There was no significant effect of the treatment over time in HADS-depression score during the treatment period between participants in the two treatment conditions using MMRM (Table 6.15).

Methamphetamine Craving

Craving symptoms were measured by using the BSCS scales. There were statistically significant differences in the BSCS score between patients in the aripiprazole group and those in the placebo group on visit day 28, day 42 and day 56 (Table 6.14). There were also

7 Overall Conclusions and Recommendations

statistically significant effects of the intervention using the BSCS scales in the MMRM (Table 6.15).

Adverse Events

Adverse events (AEs) reported in both groups were all mild to moderate in intensity. No serious AEs occurred during the study. There were no significant differences in the incidence of AEs between the aripiprazole arm and the placebo arm in any of the AEs (Table 6.7). In the aripiprazole arm, akathisia, insomnia and agitation were the three most common AEs reported, while in the placebo arm, psychosis and insomnia were the two most common AEs reported.

Concomitant Medications

There were 7 patients from the aripiprazole arm received concomitant medications and 3 from the placebo arm receive concomitant medications. Medications given were: lorazepam to treat agitation, akathisia and insomnia; zolpidem to treat insomnia; and escitalopram to treat depression (Table 6.8).

BARS, SAS and AIMS

The BARS, SAS and AIMS scores were shown in Table 6.9 and Table 6.10. There were no statistically significant changes between the aripiprazole and placebo arm for all the scales.

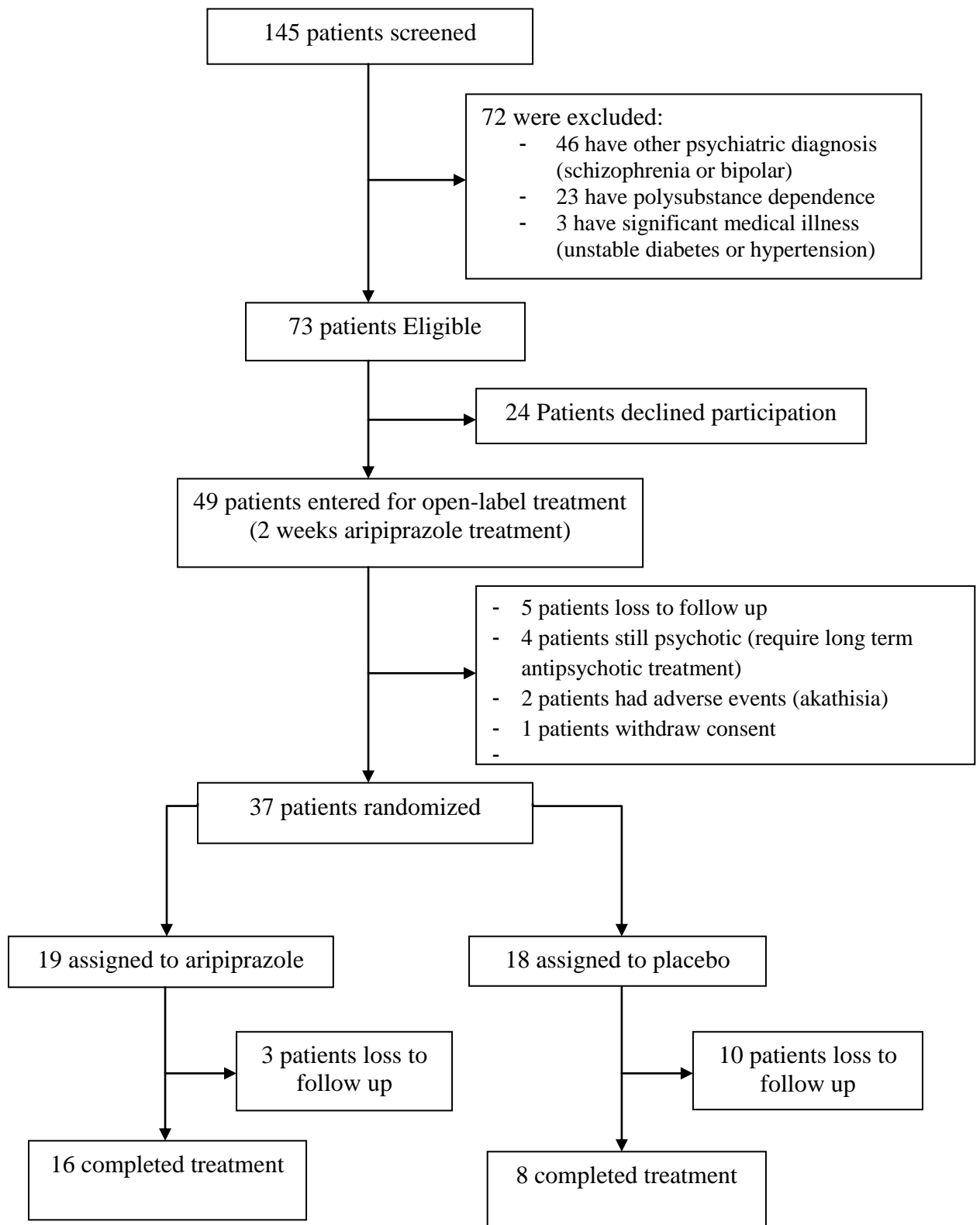
7 Overall Conclusions and Recommendations

Aripiprazole Dosage

The average mean dose for aripiprazole during the study was shown in Table 6.11. The patients were started on 10 mg aripiprazole at baseline, and were given flexible doses of 5-10 mg/day during the 8-week study.

7 Overall Conclusions and Recommendations

Figure 6.4 Disposition of patients in the randomized controlled trial between aripiprazole and placebo for methamphetamine dependence patients



7 Overall Conclusions and Recommendations

Table 6.3 Sociodemographic characteristics of methamphetamine dependence subjects

Variables	Aripiprazole (n=19)	Placebo (n=18)	p value
Age , mean \pm SD	35.5 \pm 8.5	32.9 \pm 8.4	p >0.05
Gender, %			
Male	94.7 (18)	94.4 (17)	p >0.05
Female	5.3 (1)	5.6 (1)	
Ethnic, %			
Malay	57.9 (11)	72.2 (13)	p >0.05
Chinese	31.6 (6)	16.7 (3)	
‡Indian	10.5 (2)	11.1 (2)	
Marital Status, %			
‡Married	42.1 (8)	44.4 (8)	p>0.05
Single	42.1 (8)	38.9 (7)	
Divorced	15.8 (3)	16.7 (3)	
Education, %			
‡Tertiary	11.2 (2)	16.7 (3)	p>0.05
Secondary	77.8 (14)	77.7 (14)	
Primary	11.1 (2)	5.6 (1)	
Employment, %			
Full time	78.9 (15)	83.3 (15)	p >0.05
Part time	0	5.6 (1)	
Student	0	5.6 (1)	
‡Unemployed	21.4 (4)	5.6 (1)	
Income, mean \pm SD (in Ringgit Malaysia per month)	8,047 \pm 23,172	3,441 \pm 4,801	p >0.05¶
Number of sibling, mean \pm SD	4.9 \pm 2.8	5.5 \pm 2.5	p >0.05

‡Reference group

¶Mann-Whitney U Test

7 Overall Conclusions and Recommendations

Table 6.4 Drug history of methamphetamine dependence subjects

Variables	Aripiprazole (n=19)	Placebo (n=18)	p value
Years methamphetamine used, mean \pm SD	5.5 \pm 4.8	4.8 \pm 3.6	p>0.05
Age of first methamphetamine used, mean \pm SD	30.8 \pm 8.2	28.2 \pm 9.2	p>0.05
Amount of money spend monthly for methamphetamine, mean \pm SD in Ringgit Malaysia	1,311 \pm 1,320	1,611 \pm 2,295	p>0.05¶
Route of methamphetamine, (%)			
Smoking	61.1 (11)	55.6 (10)	p>0.05
Nasal	27.8 (5)	38.9 (7)	
¶Oral	8.3 (3)	5.6 (1)	
Nicotine dependence,(%)	83.3 (15)	88.9 (16)	p>0.05
Alcohol abuse,(%)	5.3 (1)	5.6 (1)	p>0.05
Cannabis abuse,(%)	27.8 (5)	50.0 (9)	p>0.05

¶Reference group

¶¶Mann-Whitney U Test

7 Overall Conclusions and Recommendations

Figure 6.5 Methamphetamine positive urine screens by visit

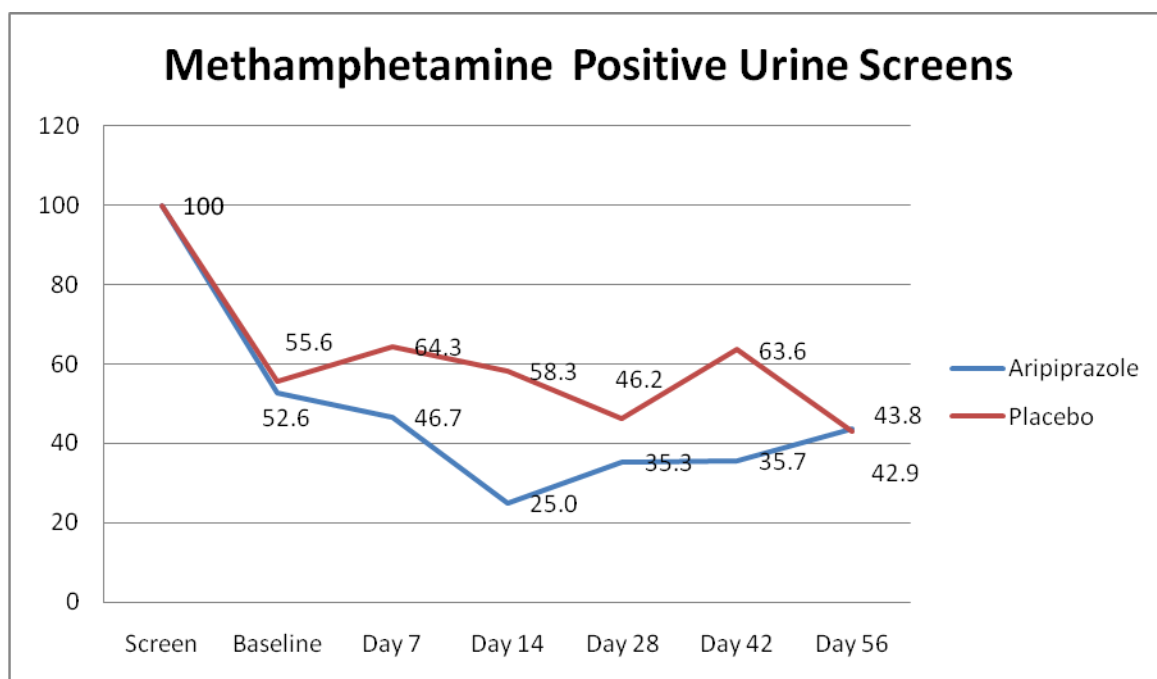


Table 6.5 Proportion of methamphetamine-positive urine screens for aripiprazole and placebo

Visits	Aripiprazole (n=19)	Placebo (n=18)
Screening Visit	100 (19/19)	100(18/18)
Baseline	52.6 (10/19)	55.6 (10/18)
Day 7	46.7 (7/15)	64.3 (9/14)
Day 14	25.0 (4/16)	58.3 (7/12)
Day 28	35.3 (6/17)	46.2 (6/13)
Day 42	35.7 (5/14)	63.6 (7/11)
Day 56	43.8 (7/16)	42.9(3/7)

7 Overall Conclusions and Recommendations

Table 6.6 Generalized Estimating Equations(GEE) analysis for methamphetamine urine screens between aripiprazole and placebo

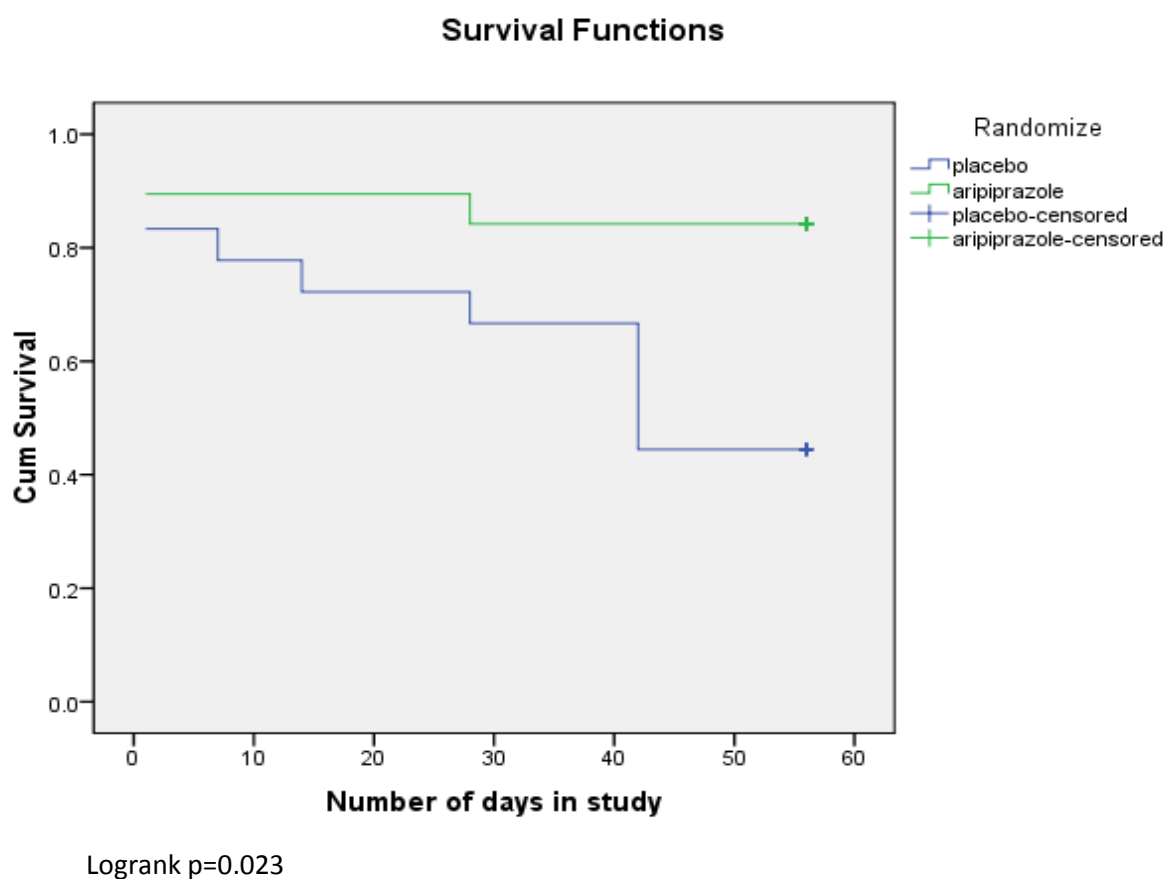
Source	Type III		
	Wald Chi-Square	df	Sig.
(Intercept)	0.36	1	0.549
Visit	3.75	4	0.441
Group	1.86	1	0.173
Visit * Group	3.94	4	0.415

Dependent Variable: Urine

Model: (Intercept), Visit (Baseline, day 7,14, 28, 42 and 56), Group (aripiprazole and placebo), Visit * Group

7 Overall Conclusions and Recommendations

Figure 6.6 Kaplan-Meier estimate of the survivor function for retention in treatment



Means and Medians for Survival Time

Randomize	Mean	95% C.I.	Median	95% C.I.
Placebo	37.11	(27.14, 47.09)	42.0	(27.54, 56.46)
Aripiprazole	48.74	(40.86, 56.62)		
Overall	43.08	(36.50, 49.67)		

7 Overall Conclusions and Recommendations

Table 6.7 Number (%) of patients reporting adverse events – safety population

Adverse Events	Aripiprazole (n=19)	Placebo (n=18)
Akathasia	26.6 (5)	5.6(1)
Insomnia	10.6 (2)	11.1 (2)
Agitation	10.6 (2)	5.6 (1)
Urinary Retention	5.3 (1)	0
Depression	5.3 (1)	0
Psychosis	0	22.2 (4)
Lethargy	0	5.6 (1)
Sedation	0	5.6 (1)
Sexual Dysfunction	0	5.6 (1)

p > 0.05 on all items

Table 6.8 Concomitant medications and the indication according to treatment group

Concomitant Medication /Indication	Aripiprazole (n=19)	Placebo (n=18)
Lorazepam / Agitation	5.3 (1)	5.6 (1)
Lorazepam/Akathasia	21.2 (4)	0
Lorazepam / Insomnia	0	11.2 (2)
Zolpidem / Insomnia	5.3 (1)	0
Escitalopram / Depression	5.3 (1)	0

7 Overall Conclusions and Recommendations

Table 6.9 BARS safety measures - changes from baseline at day 14, and day 42

BARS	Aripiprazole (n=19)	Placebo (n=18)	95% CI (p value)
Baseline	1.0 ± 2.5	0.1 ± 0.5	-2.2, 0.3 (p>0.05)
Day 14	0.6 ± 1.5	0	-1.3,0.1 (p>0.05)
Day 42	0.6 ± 1.5	0	-1.3,0.1 (p>0.05)

Table 6.10 SAS and AIMS safety measures - changes from baseline at day 14, and day 42

SAS/AIMS	Aripiprazole (n=19)	Placebo (n=18)
Baseline	0	0
Day 14	0	0
Day 42	0	0

Table 6.11 Aripiprazole dosage among the methamphetamine dependence patients

Visits	Aripiprazole (n=19)
Baseline(Starting Dose)	10mg/day
Day 7	9.6 ± 3.5
Day 14	8.7 ± 3.0
Day 28	7.8 ± 2.7
Day 42	7.3 ± 3.3
Day 56	7.9 ± 4.5

7 Overall Conclusions and Recommendations

Table 6.12 PANSS and CGI efficacy measure for psychotic symptoms

	Aripiprazole (n=19)	Placebo (n=18)	95% CI (p value)
PANSS, mean \pm SD			
Baseline	44.9 \pm 10.6	45.8 \pm 12.2	-6.8, 8.4 (p>0.05)
Day 14	40.9 \pm 10.2	51.6 \pm 20.8	-0.2, 21.5 (p>0.05)
Day 56	38.0 \pm 10.0	51.0 \pm 20.8	2.2, 23.8 (p=0.02)*
CGI, mean \pm SD			
Baseline	2.0 \pm 0.9	2.1 \pm 0.9	-0.5, 0.7 (p>0.05)
Day 14	1.7 \pm 0.9	2.5 \pm 1.3	0.01,1.5 (p=0.04)*
Day 56	1.3 \pm 0.6	2.4 \pm 1.2	0.5,1.8 (p=0.004)*

Table 6.13 Mixed Model Repeated Measures (MMRM) for PANSS and CGI among methamphetamine dependence patients

Source	PANSS		CGI	
	F	Sig.	F	Sig.
Intercept	413.74	0.001	182.54	0.001
Intervention * Time	6.26	0.004	4.12	0.021
Intervention	4.94	0.032	6.30	0.017
Time	0.19	0.825	1.66	0.200

Dependent Variable: PANSS and CGI

Model: (Intercept), Time (Baseline, day 14 and 56), Intervention (aripiprazole and placebo), Intervention * Time

7 Overall Conclusions and Recommendations

Table 6.14 Brief Substance Craving Scale (BSCS) efficacy measures, HADS efficacy measures for anxiety and depressive symptoms.

	Aripiprazole (n=19)	Placebo (n=18)	95% CI (p value)
HADS- Anxiety			
Baseline	2.6 ± 2.8	3.6 ± 3.3	-1.1, 3.0 (p>0.05)
Day 14	1.7 ± 2.2	4.9 ± 4.2	0.9, 5.4 (p=0.009)*
Day 42	1.5 ± 1.9	3.6 ± 3.7	0.1, 4.0 (p=0.04)*
HADS-Depression			
Baseline	2.5 ± 3.6	3.8 ± 4.5	-1.4, 3.9 (p>0.05)
Day 14	1.7 ± 2.8	4.7 ± 4.6	0.4, 5.4 (p=0.02)*
Day 42	2.1 ± 2.8	3.4 ± 3.9	-0.1, 3.6 (p>0.05)
BSCS			
Baseline	2.5 ± 2.9	2.3 ± 2.7	-0.5, 3.2 (p>0.05)
Day 7	1.6 ± 2.7	2.0 ± 2.9	- 1.4, 5.2 (p> 0.05)
Day 14	2.3 ± 3.0	2.5 ± 3.2	- 0.5, 4.9 (p>0.05)
Day 28	1.9 ± 2.8	4.6 ± 2.7	0.7, 4.5 (p=0.007)*
Day 42	1.8 ± 2.8	4.4 ± 3.1	0.7, 4.7 (p=0.01)*
Day 56	1.5 ± 2.3	4.5 ± 2.9	1.3, 4.8 (p=0.001)*

Table 6.15 Mixed Model Repeated Measures (MMRM) for HADS-Anxiety, HADS-Depression and BSCS among methamphetamine dependence patients

Source	HADS-Anxiety		HADS-Depression		BSCS	
	F	Sig.	F	Sig.	F	Sig.
Intercept	44.54	0.001	33.03	0.001	42.11	0.001
Intervention * Time	3.48	0.037	1.364	0.264	1.62	0.159
Intervention	6.68	0.014	3.67	0.063	6.51	0.015
Time	2.87	0.065	0.54	0.584	1.73	0.133

Dependent Variable: HADS-Anxiety, HADS-Depression and BSCS

Model for HADS-Anxiety and HADS-Depression : (Intercept), Visit (Baseline, day 14 and 42), Intervention (aripiprazole and placebo), Intervention * Time

Model for BSCS: (Intercept), Time (Baseline, day 7,14, 28, 42 and 56), Intervention (aripiprazole and placebo), Intervention * Time

7 Overall Conclusions and Recommendations

6.5 Discussion

In this randomised, placebo-controlled trial of the safety and efficacy of aripiprazole in the treatment of methamphetamine dependence, patients still continued taking the stimulant drug despite treatment. Our study showed that aripiprazole was not significantly more effective than placebo in reducing methamphetamine use, as reflected in the urine screening results that showed no statistically significant difference between the aripiprazole and placebo groups on the number of urine positive samples. The inability of this study to detect any statistical significant difference in the urine screening results could possibly be due to the small sample size of the study.

No differences were observed in the depression scores between the active treatment and placebo. Aripiprazole has been used alone or with other medications to treat manic-depressive disorder, and also been used with an antidepressant to treat depression when symptoms cannot be controlled by the antidepressant alone (Keck *et al.*, 2007, Marcus *et al.*, 2008). In this study, aripiprazole did not show significant effects in reducing the depressive symptoms scores in the methamphetamine dependent subjects. This is probably because the mean score for the depressive items in the HADS scale was already low in both placebo and aripiprazole group at baseline. To obtain a significant difference we probably need to study a bigger sample and follow up the patients over a longer period.

7 Overall Conclusions and Recommendations

However, results favouring the aripiprazole group were found on the other primary outcome measure and four of the five tertiary study endpoints investigated in this study, namely significantly better retention in treatment, improved psychotic symptoms (as measured with PANSS and CGI), improved craving symptoms and improved anxiety symptoms.

Even though some patients in the aripiprazole arm remained dependent on methamphetamine, the majority of them returned for the scheduled evaluation visits, with only 3 patients lost to follow up. This has a good clinical implication. As shown by studies, psychosocial interventions, such as cognitive behavioural therapy, contingency management and the matrix model approach, may provide significant benefit to psychostimulant users (Shoptaw *et al.*, 2006, Aharonovich *et al.*, 2003, Baker *et al.*, 2005, Rawson *et al.*, 2004). One of the most significant problems for the long-term treatment of stimulant dependence is the high incidence of relapse to drug seeking and drug taking following prolonged periods of abstinence (Dackis and O'brien, 2001, Wagner and Anthony, 2002). By being able to be retained in the treatment for a longer duration, patients have a greater opportunity to receive frequent health services provided by their doctors and therefore can be given psychological or behavioural therapies to improve treatment outcome.

Aripiprazole is an antipsychotic agent already proven to be successful in the pharmacological treatment of positive symptoms in schizophrenia (Taylor, 2003). Our results concurred with that by

7 Overall Conclusions and Recommendations

demonstrating the significant effects of aripiprazole on psychotic symptoms among methamphetamine dependent patients in this study. Both the PANSS and CGI scores decreased significantly in the aripiprazole-treated subjects, while increased in the placebo group. Patients enrolled into our study had an average CGI score of 2.0 and 2.1 in the aripiprazole and placebo groups, respectively at baseline. The scores reduced to normal in the aripiprazole arm while showing a worsening trend in the placebo group. In fact, four patients in the placebo arm (22.2%) developed worsening of psychotic symptoms during the study.

The positive symptoms in schizophrenia are hypothesised to result from excess subcortical dopamine release (Taylor, 2003). Disturbed mesolimbic dopamine neurotransmission is believed to play a major role in psychostimulant dependence (Pulvirenti and Koob, 2002). It is possible that aripiprazole counteract the high dopamine levels found during the bingeing periods of the dependence cycle that caused the psychotic symptoms, and thus exert its effect on those symptoms.

Our study also noted that aripiprazole might have effects on anxiety symptoms presented in the methamphetamine dependent patients undergoing treatment. Significant differences in the anxiety items scores of the HADS could be seen between patients in the aripiprazole group and those in the placebo group. This finding corresponds to results from studies of aripiprazole in treating refractory generalised anxiety disorder (Hoge *et al.*, 2008) or anxiety symptoms in depressed patients (Adson *et al.*, 2005).

7 Overall Conclusions and Recommendations

It is not clear why antipsychotic medications may have a positive effect on symptoms of anxiety. The second-generation antipsychotics have an effect on both the dopaminergic and serotonergic systems. Both of these neurotransmission pathways have been implicated in both depression and anxiety, and agents that have an effect on these systems may ameliorate these symptoms (Stein *et al.*, 2002). The anxiolytic effects of aripiprazole may be given rise from its activity at the serotonin 1A (5-HT^{1A}) receptor (Carli *et al.*, 1993, Collinson and Dawson, 1997), and its partial agonist and dopaminergic stabilising qualities (Adson *et al.*, 2005).

In this study we found that aripiprazole might be effective in reducing methamphetamine craving. There were significant differences in the BSCS score between patients in the aripiprazole group and those in the placebo group. Previous study supported that aripiprazole was able to reduce craving among schizophrenic with cocaine dependence (Beresford *et al.*, 2005). However our findings did not support an earlier study by Newton *et al.* (Newton *et al.*, 2008) that compared aripiprazole (15 mg) with placebo in the treatment of methamphetamine addiction. They found that aripiprazole treatment has no effect on methamphetamine craving, whether it was cue-induced or daily baseline. The difference could be due to the lower dosage that was used in our study. There are few studies that suggested using a lower dosage of aripiprazole (Newton *et al.*, 2008, Stoops, 2006, Stoops *et al.*, 2006).

7 Overall Conclusions and Recommendations

All in all, the strategy to use a partial agonists in mediating the receptor system may be an effective treatment for stimulant dependence (Childress and O'brien, 2000). During initial abstinence from chronic stimulant administration, the dopamine tone is low (Weiss *et al.*, 1992). A partial agonist such as aripiprazole produces some stimulation at the D2 receptors, and may therefore act as a replacement medication. When there are higher levels of neurotransmitter present in the synapse, as would occur following the use of methamphetamine upon relapse, aripiprazole act as an antagonist. Therefore using aripiprazole to treat methamphetamine dependence may be able to block the acute stimulant abuse-related effects, thereby extinguishing drug-seeking and drug-taking behaviours over time. However, Lile *et al* (Lile *et al.*, 2005) pointed out there is an inherent limitation to the use of competitive antagonist to treat drug dependence. If drug-dependent patients are maintained on a competitive antagonist, they may increase self-administration of the stimulant drug to offset the effects of the antagonist (withdrawal symptoms), leading to continued use of the stimulant. This could be a possible reason to some of patients in this study continued to use methamphetamine while on aripiprazole treatment.

Nevertheless, our study shows that aripiprazole can be safely administered to subjects dependent on a stimulant. In general, atypical antipsychotics are less likely to cause movement-related side effects, such as tardive dyskinesia, but may be associated with other adverse effects, including weight gain, sedation, increased levels of prolactin,

7 Overall Conclusions and Recommendations

and glucose and lipid dysregulation (Srisurapanont *et al.*, 2004, Hunter *et al.*, 2003). Earlier research that compared aripiprazole with other atypical antipsychotics found there was less weight gain, no hyperprolactinaemia and lower risk for diabetes and hyperlipidaemia with aripiprazole (Mcquade *et al.*, 2004, Marder *et al.*, 2003, Chrzanowski *et al.*, 2006).

In our study, aripiprazole appeared to be safe and well tolerated for the treatment of methamphetamine dependence. No medication-related serious AE was reported in patients treated with aripiprazole. Nevertheless, there were incidences of mild-to-moderate and transient akathisia and agitation in both treatment arms, with the aripiprazole arm reporting a higher incidence than in the placebo group.

When comparing the scores of BARS, AIMS, and SAS between the two treatment groups, no significant differences were noted.

There might be conjectures that the dose of aripiprazole used in this study was low to elicit apparent effect. However, an earlier study by Stoops and colleagues (Stoops *et al.*, 2006) showed that 10 mg aripiprazole is a reasonable starting dose for the treatment of stimulant abuse and dependence. In their study, aripiprazole given at 10 mg was not effective at attenuating the discriminative-stimulus effects of d-amphetamine in healthy volunteers, but was able to reduce some positive subject-rated effects produced by d-amphetamine. This may explain why aripiprazole, albeit given at a lower dose, was able to attenuate some of the behavioural effects of methamphetamine

7 Overall Conclusions and Recommendations

dependent patients in our study, resulting in better retention rates compared to placebo.

Two previous studies (Tiihonen *et al.*, 2007, Newton *et al.*, 2008) that compared aripiprazole and placebo showed that the antipsychotic failed to treat methamphetamine dependence. Unlike their studies, this study managed to show that aripiprazole is at least significantly more effective than placebo in keeping patients in treatment, improving psychotic and anxiety symptoms. The difference in our findings and theirs may possibly due to several differences in the study designs, in terms of the study population, route of administration of methamphetamine and dosage used.

This study included subjects who are methamphetamine-dependent with psychotic symptoms, whereas the subjects from the earlier two studies did not present with psychotic symptoms. The subjects in our study are more likely to represent the type of patients physicians see in the real clinical settings.

The study population in the previous studies used intravenous methamphetamine while patients in our study used methamphetamine via the smoking/nasal and oral routes. Different routes of methamphetamine administration may have different pharmacological effects that resulted in the urge for repeated use of the stimulant.

Ethnic differences could also account for the disparity between this study and the other two. Their studies involved Caucasian subjects while ours were an Asian sample. The pharmacokinetics and

7 Overall Conclusions and Recommendations

pharmacodynamics of aripiprazole may vary across different ethnic populations.

In terms of dosage, our study used a lower and flexible dose of 5-10 mg of aripiprazole once daily. The earlier studies used 15 mg fixed dose. The more intense withdrawal symptoms caused by a higher dose of aripiprazole might have possibly 'forced' patients to increase methamphetamine use to overcome those symptoms in one of the studies (Tiihonen *et al.*, 2007). Patients in our study also underwent detoxification for 2 weeks with aripiprazole and other symptomatic treatment (e.g. benzodiazepine) prior to randomisation to aripiprazole or placebo.

The patients in this study have severe dependence and had at least 3 months of history of drug use; this population was practically similar to that found in real-life settings. Therefore this study can be considered more of an effectiveness study rather than an efficacy study alone.

Considering all outcomes in this study, aripiprazole was effective in retaining patients in treatment, reducing methamphetamine cravings, improving psychotic and anxiety symptoms, but was not effective in reducing depressive symptoms and maintaining abstinence in our study population. We cannot as yet draw any definite conclusion on its potential efficacy in relapse prevention among detoxified patients. Future research to include more patients and with a longer study duration is needed to ascertain the therapeutic effect of aripiprazole in methamphetamine dependence.

7 Overall Conclusions and Recommendations

Limitation and Errors

While the present results suggest that aripiprazole may have clinical utility in the management of methamphetamine abuse dependence, several limitations related to the study design should be acknowledged. The primary limitations of this study include a small sample size, the relatively short study duration, and the omission of behavioural measures of reinforcing effects of methamphetamine.

i). Adequacy of Sample Size

Although the required sample size was 18 per arm and maintained 80% power of the study, the small sample size (aripiprazole n=19, placebo n=18) might have precluded detection of any but statistically large effects.

We are not able to enroll a larger number of samples due to financial limitations. We were only given a small amount of study grants (RM150,000) by University of Malaya. In order to get more samples, we need to open up more study sites, hire more investigators and study coordinators, do more advertisement in mass media and have enough funds to buy the study medications.

ii). Conduct of study

For blinding in this study, the original form of medications (aripiprazole and vitamin B complex) was repacked in the capsule. Patient might open the capsule and know their assignment either study medication or placebo, this might interfere with the compliance.

7 Overall Conclusions and Recommendations

Additionally, it might take a longer than 8 weeks to achieve full benefit from aripiprazole treatment. Again, we could not do a longer follow up study because of financial limitations. We only have enough funds to follow up patients up to 8 weeks.

iii). Representative and Generalisation

The findings of this study could only be generalized with caution because the study population was from the inpatient and outpatient clinic located in a hospital in Kuala Lumpur. The study population differs from the patients in the community because of the treatment seeking behavior. To make generalized inferences of the findings of this study to the methamphetamine dependence patients in community would be inappropriate because the setting in this study had introduced selection bias.

For a better generalization of the findings, it would be ideal to conduct a community survey. Unfortunately, such a study is not feasible to be conducted due to the legal implication.

iv). Instruments of the study

All the scales have been used widely in this country however until now, there was no paper being published regarding the validation of the scales in the local population.

v). Comparing Findings With Other Studies

Comparison of the findings of this study to other studies may be inaccurate, although other studies examined the same variables, but

7 Overall Conclusions and Recommendations

the inclusion and exclusion criteria used to identify subjects or sampled population could differ, or study could be conducted with different study design.

No behavioural measures of reinforcement intervention were incorporated into the design of this study. While treatments medications are intended to reduce drug-taking behaviour, other studies have proven that modification of subjective effects requires behavioural measures of reinforcement, e.g. drug self-administration or the multiple-choice procedure (Fischman and Schuster, 1982, Griffiths *et al.*, 1993). Our future research would possibly incorporate behavioural therapy, but the administration of pharmacotherapy and behavioural therapy should be approached in a systematic way (Vocci and Appel, 2007) , as the medication may interact selectively with a certain type of behavioural therapy (Poling *et al.*, 2006, O'malley *et al.*, 1992).

6.6 Conclusions

Aripiprazole was no more effective than placebo in maintaining abstinence from methamphetamine use. However, it facilitated treatment retention and reduced the occurrence of psychotic symptoms in this study population. Aripiprazole was generally safe and well tolerated. It might have a role in the treatment of methamphetamine dependence with psychotic symptoms.

7 Overall Conclusions and Recommendations

Chapter SEVEN: Overall Conclusions and Recommendations

7.1 Overall Conclusions

Methamphetamine dependence and its psychiatric sequelae are increasingly rampant in Malaysia. The widespread occurrence of methamphetamine dependence has brought an impact that can be felt at various levels, from the individual, to the individual's family, community and society. At the country level, methamphetamine dependence gives rise to serious behavioural, medical and psychiatric consequences, imposing an immense burden on the medical, public health and criminal justice systems.

Unfortunately there are not many studies done on the issues of methamphetamine dependence in Malaysia. We are still lacking in data especially in terms of prevalence, psychiatry morbidity, genetic risk factors and treatment aspect. Before effective strategy and treatment plan can be devised to curb this public health and social burden of the country, an understanding of the issue is warranted.

7.1 1 Prevalence of Psychiatric Comorbidity and Suicidality

The co-occurrence of psychiatric disorder and substance dependence disorder is a common condition (Wilson, 2007). The presence of a psychiatric disorder increases the risk for the presence of substance dependence disorder and vice-versa (Swendsen *et al.*, 2010). Much evidence suggest that when these disorders occur together, is

7 Overall Conclusions and Recommendations

associated with worse health outcomes, more complex clinical management, and increased health care costs (Wilson, 2007).

We investigated the prevalence of psychiatric co-morbidity and the prevalence of suicidality in methamphetamine dependence patients. We also wanted to determine the association between psychiatric co-morbidity and suicidality.

The prevalence of psychiatric co-morbidity was 54.4% and the prevalence of suicidality in methamphetamine dependence patients was 12.1%. Our study demonstrated that methamphetamine dependence in Malaysians have high psychiatric comorbidity, with antisocial personality disorder being the most prevalently diagnosed comorbidity. Psychiatric comorbidities that were significantly associated to suicidality in methamphetamine dependence were depression, schizophrenia, panic disorder, and current and lifetime psychotic disorder.

The observations from our study supported findings of earlier studies that methamphetamine-dependent individuals are at greater risk of experiencing particular psychiatric symptoms (Kalechstein *et al.*, 2000, Yen and Chong, 2006, Chen *et al.*, 2003), and are more likely to experience depressive symptoms and suicidal ideation than non-methamphetamine dependent individuals. Data from our study and studies of other researchers, suggest that when treating methamphetamine-dependent individuals, a careful assessment of psychiatric history and assessment of suicidal risk are warranted.

7 Overall Conclusions and Recommendations

7.1.2 Prevalence and Association of Methamphetamine Induce Psychosis

When used in high dose or repeatedly, methamphetamine can cause drug-induced psychosis that display symptoms similar to those of paranoid schizophrenia, which is characterised by hallucinations, delusions and thought disorders. Methamphetamine induced psychosis is one of the most widely known side effects associated with high-dose or chronic methamphetamine use (Griffith *et al.*, 1972, Hall *et al.*, 1996). In general, psychotic symptoms induced by substance use resolve within hours or days after withdrawal from the drug (transient type), but they may be significantly prolonged (persistent type) in some individuals, despite the absence of a known prior history of psychotic illness.

The aims of this study were to investigate the prevalence of psychosis among methamphetamine dependent patients and to investigate the associated factors.

Our results showed that 47.9% of the subjects had at least one episode of psychotic symptoms after they were dependent on methamphetamine. 13.0% of the patients were still having psychotic symptoms at the time of assessment. Persecutory delusions, auditory hallucinations, strange or unusual belief and delusions of reference were the most common symptoms. Our results concur with finding from other investigators. In a cross-country study including Australia, Japan, Philippines and Thailand where psychotic symptoms in methamphetamine psychotic in-patients were evaluated using the Mini-

7 Overall Conclusions and Recommendations

International Neuropsychiatric Interview found high prevalence rate of lifetime and current psychotic symptoms (Srisurapanont *et al.*, 2003).

After multiple logistic regression, the independent risk factors of psychosis were mania, antisocial personality disorder, higher amount of stimulant use and higher family income.

The prevalence of psychosis among methamphetamine dependent subjects was found to be alarmingly high in our study. These findings substantiate the fact that methamphetamine users are a high-risk population for psychosis, including those without known history of schizophrenia or other psychotic disorders.

7.1.3 Association of Brain-Derived Neurotrophic Factor (Val66Met) Genetic Polymorphism with Male Methamphetamine Dependence in Malaysia.

Methamphetamine abuse can lead to drug dependence when taken often enough and in large enough quantities. However, individuals are differentially vulnerable to methamphetamine dependence. The probability of continuing drug use varies from individual to individual, and the difference is very likely due to both biological and psychosocial factors.

Familial and population genetic studies (Mirin *et al.*, 1991, Rounsaville *et al.*, 1991, Luthar and Rounsaville, 1993) have revealed possible genetic bases for some of the inter-individual differences in vulnerability to substance abuse and addiction risk. The susceptible single nucleotide polymorphisms (SNP) in some genes may contribute

7 Overall Conclusions and Recommendations

to addiction vulnerability in several ways, including changing the structure or function of specific proteins. A mutant protein causes structural or functional changes of specific brain circuits during development phase or in adulthood (Nestler, 2000). These altered brain circuits may change an individual's responsiveness to initial drug exposure, or alter the adaptations that occur in the brain after repeated drug exposure.

Brain-derived neurotrophic factor (BDNF), a member of the nerve growth factor-related family of neurotrophins, is widely expressed in the adult mammalian brain. Evidence indicates that BDNF may be involved in the mechanisms underlying substance abuse (Hofer *et al.*, 1990). BDNF plays an important role in the neurodevelopment of dopaminergic (DA)-related systems. Recent studies have demonstrated that the BDNF gene is associated with vulnerability to drug abuse (Itoh *et al.*, 2005).

We investigated (i) the association of the BDNF gene Val66Met polymorphism with methamphetamine dependence (ii) the association of the BDNF gene Val66Met polymorphism with the occurrence of psychosis among methamphetamine dependence patients in a Malaysian male population with different ethnicities.

186 male methamphetamine-dependent subjects and in 154 male controls of four different ethnicities, namely, Malay, Chinese, Kadazan-Dusun, and Bajau were recruited in this study. Our results showed that the distribution of the BDNF Val66Met genotype in Chinese subjects with methamphetamine dependence and methamphetamine psychosis

7 Overall Conclusions and Recommendations

were significant compared with controls. The frequency of the 66Val allele in methamphetamine-dependent subjects was higher than that in the control group, suggesting that the 66Val carriers are more susceptible to methamphetamine dependence.

However, 66Val allele frequency in other ethnicities was not significantly different from the controls. The results of the study also showed that in the Chinese methamphetamine dependent subjects, there was a difference in allele frequency when comparing those who developed psychosis and those who did not.

Our findings suggest that the BDNF Val66Met polymorphism may contribute to methamphetamine dependence and psychosis in the Chinese population but not in other Malaysian ethnicities.

7.1.4 Efficacy and Safety of Aripiprazole in the Treatment of Methamphetamine Induce Psychosis: An Open Label Prospective Study

Although methamphetamine induced psychiatric disorders are typically self-limited and usually abate on their own, treatment is still needed in cases of emergency situations (i.e. acute episodes of methamphetamine induced psychosis), as well as to prevent recurrence in long-term. Recurrence of psychotic symptoms can occur due to continued use of methamphetamine or other drug use and also due to psychosocial stressors (Yui *et al.*, 1997, Yui *et al.*, 2000). In some cases psychosis may persist and around 5 -15% of users who developed methamphetamine psychosis fail to recover completely

7 Overall Conclusions and Recommendations

(Hofmann, 1983). When the psychotic symptoms persist and interfere with the patient's social and occupational functioning, treatment should be targeted to psychiatric symptoms present (Larson, 2008).

The objective of this study was to explore the therapeutic effects and tolerability of aripiprazole in the occurrence of psychosis among methamphetamine dependent patients.

A total of 49 patients were enrolled and started on aripiprazole out of which 83.7% completed the study. There was a statistically significant decline in the mean PANSS-total and CGI-S score over the course of the study. Aripiprazole was generally well tolerated during the study. Adverse events were reported in 20.4% of patients. The reported adverse events were akathisia, insomnia, agitation, sedation and depression. Most adverse events were mild to moderate in intensity. There was no serious adverse event during the study period.

This 2-week, open-label study shows that aripiprazole given once-daily improved the psychotic symptoms associated with methamphetamine dependence. The treatment was generally well tolerated with mild to moderate adverse events. In this study aripiprazole was an efficacious and safe option for the treatment of methamphetamine-induced psychosis.

7 Overall Conclusions and Recommendations

7.1.5 Randomized Placebo-Controlled Trial of the Safety and Efficacy of Aripiprazole in the Treatment of Methamphetamine Dependence Patients

There are great needs in the treatment of methamphetamine dependence. The goals of drug dependence treatment are to reduce further drug use, improve the patient's ability to function, minimize the medical and social complications of drug abuse and dependence, and ultimately to achieve lasting abstinence (Kay-Lambkin *et al.*, 2010). Managing methamphetamine dependence, as well as to recover from it, does not involve a brief detoxification and discharge, but a long-term process to help individuals free themselves from illicit substance use (Bruce, 2000).

The objective of this study was to determine the efficacy and safety of aripiprazole among methamphetamine dependence patients.

84.2% of participants randomized to aripiprazole completed the 8 weeks study compared to only 50% of the placebo group completed the study ($p < 0.05$). There was a statistically significant difference between groups in the amount of time spent in treatment, with those given aripiprazole retained for an average of 48.7 days (± 4.0) compared with only 37.1 days (± 5.0) for the placebo group. The survival curves results showed that participants in the aripiprazole group were less likely to drop out of the study than those in the placebo group. The difference was statistically significant ($p = 0.02$, $X^2 = 5.3$). Psychotic symptoms as measured by PANSS and CGI were decreased among participants who were randomized to aripiprazole treatment but

7 Overall Conclusions and Recommendations

those who were randomized to placebo showed an increase in the total PANSS and CGI score ($p < 0.05$). However there were no statistically significant effects for aripiprazole relative to placebo on methamphetamine use verified by urine drug screen. Aripiprazole treatment was not associated with any serious adverse event. Adverse event were generally mild and consistent with known pharmacological effects.

Aripiprazole was no more effective than placebo in maintaining abstinence from methamphetamine use. However, it facilitated treatment retention and reduced the occurrence of psychotic symptoms in this study population. Aripiprazole was generally safe and well tolerated. It might have a role in the treatment of methamphetamine dependence with psychotic symptoms.

7.2 Recommendations

1. We feel that identification and treatment of comorbid psychiatric illnesses in this population is of utmost importance. It is unethical not to screen and treat for psychiatric illnesses in this population, and cause unnecessary suffering, knowing very well the rate of psychiatric illnesses in them is high. Failure to identify comorbid psychiatric illnesses here means an opportunity for treatment is lost in a population that is otherwise difficult to reach in the community.
2. Identification and treatment of psychiatric illnesses must be addressed as the central role in relapse prevention of substance use. Comorbid psychiatric illnesses, particularly depression, are

7 Overall Conclusions and Recommendations

often associated with high rates of continued substance usage after treatment.

3. Screening for psychotic symptoms should be employed to patients with methamphetamine dependence especially for those who had history of mania, personality disorders, high amount of stimulant used and high family income.
4. All psychiatric symptoms especially psychosis and depression should be treated adequately.
5. We would like to suggest conducting genetic polymorphism study with a larger sample size in order to provide more evidence to confirm the genetic influence of BDNF in methamphetamine dependence.
6. We would like to suggest conducting genetic studies investigating other SNPs in methamphetamine dependence. This knowledge can help in future development of screening tools and pharmacogenomics treatment.
7. Aripiprazole can be used safely and effectively in the treatment of methamphetamine-induced psychosis.
8. Aripiprazole has a potential benefit and is safe for the treatment of methamphetamine dependence. We would like to suggest using aripiprazole as one of the treatment alternative in patients with methamphetamine dependence who had psychotic symptoms.
9. We would like to suggest conducting further study with a larger sample size and a longer duration of follow up to confirm the

7 Overall Conclusions and Recommendations

efficacy and safety of aripiprazole in the treatment on methamphetamine dependence.

10. We would like to recommend conducting a study which combined aripiprazole with one of the behavioural treatment method (cognitive therapy or contingency management program) to confirm if it will yield a better outcome.

Appendix A - Operational Definitions

Chapter Two: Psychiatric co-morbidity and suicidality in methamphetamine dependence

Chapter Three: Prevalence and association of methamphetamine psychosis

Age:

Age of the methamphetamine dependence patient in years at last birthday.

Race:

Ethnicity recorded in the medical case record.

Marital status:

Legal marital status either single or married, widowed or divorce as mentioned by patient during interview.

Education level:

Type of education institution last attended by the patient.

Occupation:

Patient's current occupation

Income:

The average income of the sum of household income of the family in a month mentioned by the patient.

Suicidality:

Suicidality was defined as in the present either of having thought wish to be dead or want to harm themselves or think about suicide or have a suicide plan or attempted suicide in the past month or lifetime,

Appendix A

measured by MINI International Neuropsychiatric Interview (M.I.N.I)(Sheehan *et al.*, 1998b)

Mood disorders:

Major depressive disorder and bipolar disorder in Axis I psychiatric disorders assessed by MINI International Neuropsychiatric Interview (M.I.N.I)

Anxiety disorder:

Generalised anxiety disorder, obsessive compulsive disorder, panic disorder and social phobia in Axis I psychiatric disorders assessed by MINI International Neuropsychiatric Interview (M.I.N.I)

Psychotic disorder:

The present of current or lifetime psychotic disorder.

Poly-substance use:

History of using more than one substance such as alcohol consumption and illicit drug other than nicotine.

Criminal record:

History of arrested or jailed due to illegal activities such as stealing, prostitution, fights, assault, rape, arson etc other than drugs.

Appendix B - Mini International Neuropsychiatric Interview (M.I.N.I.)

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 5.0.0 (July 1, 2006)

Appendix B M.I.N.I

Patient Name:	_____	Patient Number:	_____
Date of Birth:	_____	Time Interview Began:	_____
Interviewer's Name:	_____	Time Interview Ended:	_____
Date of Interview:	_____	Total Time:	_____

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10	
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	<input type="checkbox"/>	296.20-296.26 Single	F32.x	<input type="checkbox"/>
		Recurrent	<input type="checkbox"/>	296.30-296.36 Recurrent	F33.x	<input type="checkbox"/>
	MDE WITH MELANCHOLIC FEATURES Optional	Current (2 weeks)	<input type="checkbox"/>	296.20-296.26 Single	F32.x	<input type="checkbox"/>
				296.30-296.36 Recurrent	F33.x	<input type="checkbox"/>
B	DYSTHYMIA	Current (Past 2 years)	<input type="checkbox"/>	300.4	F34.1	<input type="checkbox"/>
C	SUICIDALITY	Current (Past Month) Risk: <input type="checkbox"/> Low <input type="checkbox"/> Medium <input type="checkbox"/> High	<input type="checkbox"/>			<input type="checkbox"/>
D	MANIC EPISODE	Current	<input type="checkbox"/>	296.00-296.06	F30.x-F31.9	<input type="checkbox"/>
		Past	<input type="checkbox"/>			
	HYPOMANIC EPISODE	Current	<input type="checkbox"/>	296.80-296.89	F31.8-F31.9/F34.0	<input type="checkbox"/>
		Past	<input type="checkbox"/>			
E	PANIC DISORDER	Current (Past Month) Lifetime	<input type="checkbox"/> <input type="checkbox"/>	300.01/300.21	F40.01-F41.0	<input type="checkbox"/>
F	AGORAPHOBIA	Current	<input type="checkbox"/>	300.22	F40.00	<input type="checkbox"/>
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	<input type="checkbox"/>	300.23	F40.1	<input type="checkbox"/>
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	<input type="checkbox"/>	300.3	F42.8	<input type="checkbox"/>
I	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	<input type="checkbox"/>	309.81	F43.1	<input type="checkbox"/>
J	ALCOHOL DEPENDENCE	Past 12 Months	<input type="checkbox"/>	303.9	F10.2x	<input type="checkbox"/>
	ALCOHOL ABUSE	Past 12 Months	<input type="checkbox"/>	305.00	F10.1	<input type="checkbox"/>
K	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	<input type="checkbox"/>	304.00-.90/305.20-.90	F11.1-F19.1	<input type="checkbox"/>
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	<input type="checkbox"/>	304.00-.90/305.20-.90	F11.1-F19.1	<input type="checkbox"/>
L	PSYCHOTIC DISORDERS	Lifetime	<input type="checkbox"/>	295.10-295.90/297.1/ 297.3/293.81/293.82/ 293.89/298.8/298.9	F20.xx-F29	<input type="checkbox"/>
		Current	<input type="checkbox"/>			
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime	<input type="checkbox"/>	296.24/296.34/296.44	F32.3/F33.3/ F30.2/F31.2/F31.5	<input type="checkbox"/>
		Current	<input type="checkbox"/>	296.24/296.34/296.44	F31.8/F31.9/F39	<input type="checkbox"/>
M	ANOREXIA NERVOSA	Current (Past 3 Months)	<input type="checkbox"/>	307.1	F50.0	<input type="checkbox"/>
N	BULIMIA NERVOSA	Current (Past 3 Months)	<input type="checkbox"/>	307.51	F50.2	<input type="checkbox"/>
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	<input type="checkbox"/>	307.1	F50.0	<input type="checkbox"/>

Appendix B M.I.N.I

O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	<input type="checkbox"/>	300.02	F41.1	<input type="checkbox"/>
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	<input type="checkbox"/>	301.7	F60.2	<input type="checkbox"/>
	Optional					

Which problem troubles you the most? Indicate your response by checking the appropriate check box(es). _____

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

- At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
- At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « bold » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « NO » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

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A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
	IS A1 OR A2 CODED YES?	➡ NO	YES

A3 Over the past two weeks, when you felt depressed or uninterested:

- | | | | |
|---|--|----|-------|
| a | Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by $\pm 5\%$ of body weight or ± 8 lbs. or ± 3.5 kgs., for a 160 lb./70 kg. person in a month)?
IF YES TO EITHER, CODE YES. | NO | YES * |
| b | Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning waking or sleeping excessively)? | NO | YES |
| c | Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day? | NO | YES * |
| d | Did you feel tired or without energy almost every day? | NO | YES |
| e | Did you feel worthless or guilty almost every day? | NO | YES |
| f | Did you have difficulty concentrating or making decisions almost every day? | NO | YES |
| g | Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? | NO | YES |

ARE 5 OR MORE ANSWERS (A1-A3) CODED YES?

NO YES *

**MAJOR DEPRESSIVE
EPISODE, CURRENT**

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4,
OTHERWISE MOVE TO MODULE B:

- | | | | |
|----|---|------|-----|
| A4 | a During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about? | ➡ NO | YES |
|----|---|------|-----|

NO YES

**MAJOR DEPRESSIVE
EPISODE, RECURRENT**

- | | |
|---|---|
| b | In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any depression and any loss of interest? |
|---|---|

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, A6e).

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (A3 = YES), EXPLORE THE FOLLOWING:

A5	a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
	b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? IF NO: When something good happens does it fail to make you feel better, even temporarily?	NO	YES
		IS EITHER A5a OR A5b CODED YES?	➡ NO	YES

A6 **Over the past two week period, when you felt depressed and uninterested:**

a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
b	Did you feel regularly worse in the morning, almost every day?	NO	YES
c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
d	IS A3c CODED YES (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
e	IS A3a CODED YES FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE 3 OR MORE A6 ANSWERS CODED YES?

NO	YES
Major Depressive Episode with Melancholic Features Current	

B. DYSTHYMIA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF PATIENT’S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1	Have you felt sad, low or depressed most of the time for the last two years?	➡ NO	YES
B2	Was this period interrupted by your feeling OK for two months or more?	NO	➡ YES
B3	During this period of feeling depressed most of the time:		
a	Did your appetite change significantly?	NO	YES
b	Did you have trouble sleeping or sleep excessively?	NO	YES
c	Did you feel tired or without energy?	NO	YES
d	Did you lose your self-confidence?	NO	YES
e	Did you have trouble concentrating or making decisions?	NO	YES
f	Did you feel hopeless?	NO	YES
	ARE 2 OR MORE B3 ANSWERS CODED YES?	➡ NO	YES
B4	Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?	<div> <div>NO</div> <div>YES</div> <div> DYSTHYMIA CURRENT </div> </div>	

C. SUICIDALITY

In the past month did you:

		NO	YES	Points
C1	Suffer any accident? IF NO TO C1, SKIP TO C2; IF YES, ASK C1a,:			0
C1a	Plan or intend to hurt yourself in that accident either passively or actively? IF NO TO C1a, SKIP TO C2; IF YES, ASK C1b,:			0
C1b	Did you intend to die as a result of this accident?			0
C2	Think that you would be better off dead or wish you were dead?			1
C3	Want to harm yourself or to hurt or to injure yourself?			2
C4	Think about suicide?			6

IF YES, ASK ABOUT THE INTENSITY AND FREQUENCY OF THE SUICIDAL IDEATION:

Frequency

Intensity

Occasionally	<input type="checkbox"/>	Mild	<input type="checkbox"/>
Often	<input type="checkbox"/>	Moderate	<input type="checkbox"/>
Very often	<input type="checkbox"/>	Severe	<input type="checkbox"/>

Can you control these impulses
and state that you will not act
on them while in this program?

Only score 8 points if response is NO. NO YES 8

C5	Have a suicide plan?			8
C6	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?			9
C7	Deliberately injure yourself without intending to kill yourself?			4
C8	Attempt suicide? Hoped to be rescued / survive <input type="checkbox"/> Expected / intended to die <input type="checkbox"/>			10

In your lifetime:

C9	Did you ever make a suicide attempt?	NO	YES	4
----	--------------------------------------	----	-----	---

IS AT LEAST 1 OF THE ABOVE (EXCEPT C1) CODED YES?

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C9)
CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS
INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT
OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDE RISK IN
THE SPACE BELOW:

NO	YES
SUICIDE RISK CURRENT	
1-8 points Low	<input type="checkbox"/>
9-16 points Moderate	<input type="checkbox"/>
≥ 17 points High	<input type="checkbox"/>

D. (HYPO) MANIC EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)


D1	a	Have you ever had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)	NO	YES
<p>IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior.</p> <p>IF NO, CODE NO TO D1b: IF YES ASK:</p>				
	b	Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	NO	YES
D2	a	Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified?	NO	YES
<p>IF NO, CODE NO TO D2b: IF YES ASK:</p>				
	b	Are you currently feeling persistently irritable?	NO	YES
IS D1a OR D2a CODED YES?			➡ NO	YES

D3 IF **D1b** OR **D2b** = YES: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE IF **D1b** AND **D2b** = NO: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

	<u>Current Episode</u>		<u>Past Episode</u>		
a	Feel that you could do things others couldn't do, or that you were an especially important person?	NO	YES	NO	YES
<p>IF YES, ASK FOR EXAMPLES.</p> <p>THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. <input type="checkbox"/> No <input type="checkbox"/> Yes</p>					
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Become so active or physically restless that others were worried about you?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

Appendix B M.I.N.I

	Current Episode		Past Episode									
D3 (SUMMARY): ARE 3 OR MORE D3 ANSWERS CODED YES (OR 4 OR MORE IF D1a IS NO (IN RATING PAST EPISODE) AND D1b IS NO (IN RATING CURRENT EPISODE)? RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE D3 SYMPTOMS. VERIFY IF THE SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.	NO	YES	 NO	YES								
D4 Did these symptoms last at least a week and cause significant problems at home, at work, socially, or at school, or were you hospitalized for these problems?	NO	YES	NO	YES								
	↓	↓	↓	↓								
THE EPISODE EXPLORED WAS A:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>								
	<i>HYPOMANIC EPISODE</i>	<i>MANIC EPISODE</i>	<i>HYPOMANIC EPISODE</i>	<i>MANIC EPISODE</i>								
IS D4 CODED NO?	<table><tr><td>NO</td><td>YES</td></tr><tr><td colspan="2"><i>HYPOMANIC EPISODE</i></td></tr><tr><td>CURRENT</td><td><input type="checkbox"/></td></tr><tr><td>PAST</td><td><input type="checkbox"/></td></tr></table>				NO	YES	<i>HYPOMANIC EPISODE</i>		CURRENT	<input type="checkbox"/>	PAST	<input type="checkbox"/>
NO	YES											
<i>HYPOMANIC EPISODE</i>												
CURRENT	<input type="checkbox"/>											
PAST	<input type="checkbox"/>											
SPECIFY IF THE EPISODE IS CURRENT OR PAST.												
IS D4 CODED YES?	<table><tr><td>NO</td><td>YES</td></tr><tr><td colspan="2"><i>MANIC EPISODE</i></td></tr><tr><td>CURRENT</td><td><input type="checkbox"/></td></tr><tr><td>PAST</td><td><input type="checkbox"/></td></tr></table>				NO	YES	<i>MANIC EPISODE</i>		CURRENT	<input type="checkbox"/>	PAST	<input type="checkbox"/>
NO	YES											
<i>MANIC EPISODE</i>												
CURRENT	<input type="checkbox"/>											
PAST	<input type="checkbox"/>											
SPECIFY IF THE EPISODE IS CURRENT OR PAST.												

E. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN E5, E6 AND E7 AND SKIP TO F1)

E1	a	Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
E2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms?	NO	YES
E4		During the worst spell that you can remember:		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
E5		ARE BOTH E3, AND 4 OR MORE E4 ANSWERS, CODED YES? IF YES TO E5, SKIP TO E7.	NO	YES <i>PANIC DISORDER LIFETIME</i>
E6		IF E5 = NO, ARE ANY E4 ANSWERS CODED YES? THEN SKIP TO F1.	NO	YES <i>LIMITED SYMPTOM ATTACKS LIFETIME</i>
E7		In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack?	NO	YES <i>PANIC DISORDER CURRENT</i>

M.I.N.I. 5.0.0 (July 1, 2006)

11

F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	NO	YES
----	--	----	-----

IF F1 = NO, CIRCLE NO IN F2.

F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO	YES
----	---	----	-----

AGORAPHOBIA
CURRENT

IS F2 (CURRENT AGORAPHOBIA) CODED NO

and

IS E7 (CURRENT PANIC DISORDER) CODED YES?

NO
YES

PANIC DISORDER
without Agoraphobia
CURRENT

IS F2 (CURRENT AGORAPHOBIA) CODED YES

and

IS E7 (CURRENT PANIC DISORDER) CODED YES?

NO
YES

PANIC DISORDER
with Agoraphobia
CURRENT

IS F2 (CURRENT AGORAPHOBIA) CODED YES

and

IS E5 (PANIC DISORDER LIFETIME) CODED NO?

NO
YES

AGORAPHOBIA, CURRENT
without history of
Panic Disorder

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES
G2	Is this social fear excessive or unreasonable?	➡ NO	YES
G3	Do you fear these social situations so much that you avoid them or suffer through them?	➡ NO	YES
G4	Do these social fears disrupt your normal work or social functioning or cause you significant distress?		

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT’S FEARS ARE RESTRICTED TO NON-GENERALIZED (“ONLY 1 OR SEVERAL”) SOCIAL SITUATIONS OR EXTEND TO GENERALIZED (“MOST”) SOCIAL SITUATIONS. “MOST” SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

EXAMPLES OF SUCH SOCIAL SITUATIONSTYPICALLY INCLUDE INITIATING OR MAINTAINING A CONVERSATION, PARTICIPATING IN SMALL GROUPS, DATING, SPEAKING TO AUTHORITY FIGURES, ATTENDING PARTIES, PUBLIC SPEAKING, EATING IN FRONT OF OTHERS, URINATING IN A PUBLIC WASHROOM, ETC.

NO

YES

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ☐

NON-GENERALIZED ☐

H. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

H1	<p>In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though you didn't want to, or fearing you would act on some impulse, or fear or superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, or hoarding, collecting, or religious obsessions.)</p> <p>(DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)</p>	<div>NO</div> <div>YES</div> <div>↓</div> <div>SKIP TO H4</div>
H2	<p>Did they keep coming back into your mind even when you tried to ignore or get rid of them?</p>	<div>NO</div> <div>YES</div> <div>↓</div> <div>SKIP TO H4</div>
H3	<p>Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?</p>	<div>NO</div> <div>YES</div> <div>obsessions</div>
H4	<p>In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?</p>	<div>NO</div> <div>YES</div> <div>compulsions</div>
<p>IS H3 OR H4 CODED YES?</p>		<div>➡ NO</div> <div>YES</div>
H5	<p>Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?</p>	<div>➡ NO</div> <div>YES</div>
H6	<p>Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?</p>	<div>NO</div> <div>YES</div> <div>O.C.D.</div> <div>CURRENT</div>

I. POSTTRAUMATIC STRESS DISORDER (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.	➡ NO	YES
I2	Did you respond with intense fear, helplessness or horror?	➡ NO	YES
I3	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?	➡ NO	YES
I4	In the past month:		
a	Have you avoided thinking about or talking about the event ?	NO	YES
b	Have you avoided activities, places or people that remind you of the event?	NO	YES
c	Have you had trouble recalling some important part of what happened?	NO	YES
d	Have you become much less interested in hobbies or social activities?	NO	YES
e	Have you felt detached or estranged from others?	NO	YES
f	Have you noticed that your feelings are numbed?	NO	YES
g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
	ARE 3 OR MORE I4 ANSWERS CODED YES?	➡ NO	YES
I5	In the past month:		
a	Have you had difficulty sleeping?	NO	YES
b	Were you especially irritable or did you have outbursts of anger?	NO	YES
c	Have you had difficulty concentrating?	NO	YES
d	Were you nervous or constantly on your guard?	NO	YES
e	Were you easily startled?	NO	YES
	ARE 2 OR MORE I5 ANSWERS CODED YES?	➡ NO	YES
I6	During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress?		

NO YES

**POSTTRAUMATIC
STRESS DISORDER
CURRENT**

J. ALCOHOL ABUSE AND DEPENDENCE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

J1	In the past 12 months , have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	➡ NO	YES
----	---	---------	-----

J2 In the past 12 months:

- | | | | |
|---|--|----|-----|
| a | Did you need to drink more in order to get the same effect that you got when you first started drinking? | NO | YES |
| b | When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation?
IF YES TO EITHER, CODE YES. | NO | YES |
| c | During the times when you drank alcohol, did you end up drinking more than you planned when you started? | NO | YES |
| d | Have you tried to reduce or stop drinking alcohol but failed? | NO | YES |
| e | On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol? | NO | YES |
| f | Did you spend less time working, enjoying hobbies, or being with others because of your drinking? | NO | YES |
| g | Have you continued to drink even though you knew that the drinking caused you health or mental problems? | NO | YES |

ARE 3 OR MORE J2 ANSWERS CODED YES?

* IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

NO	YES*
ALCOHOL DEPENDENCE CURRENT	

J3 In the past 12 months:

- | | | | |
|---|--|----|-----|
| a | Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems?
(CODE YES ONLY IF THIS CAUSED PROBLEMS.) | NO | YES |
| b | Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.? | NO | YES |
| c | Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct? | NO | YES |
| d | Did you continue to drink even though your drinking caused problems with your family or other people? | NO | YES |

ARE 1 OR MORE J3 ANSWERS CODED YES?

NO	N/A	YES
ALCOHOL ABUSE CURRENT		

K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

K1 a In the past 12 months, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?

➡
NO YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("angel dust", "peace pill"), psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA, or ketamine ("special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Any others?

SPECIFY MOST USED DRUG(S): _____

CHECK ONE BOX

ONLY ONE DRUG / DRUG CLASS HAS BEEN USED

☐

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED.

☐

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED)

☐

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE: _____

K2 Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:

a Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?

NO YES

b When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?

NO YES

IF YES TO EITHER, CODE YES.

c Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?

NO YES

d Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?

NO YES

e On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?

NO YES

Appendix B M.I.N.I

f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused you health or mental problems? NO YES

ARE 3 OR MORE K2 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

* IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER.
DEPENDENCE PREEMPTS ABUSE.

NO	YES *
SUBSTANCE DEPENDENCE CURRENT	

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE YES ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused problems with your family or other people? NO YES

ARE 1 OR MORE K3 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

NO	N/A	YES
SUBSTANCE ABUSE CURRENT		

L. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

Now I am going to ask you about unusual experiences that some people have.				BIZARRE
L1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO YES	YES
	b	IF YES OR YES BIZARRE: do you currently believe these things?	NO YES	YES ➡L6
L2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO YES	YES
	b	IF YES OR YES BIZARRE: do you currently believe these things?	NO YES	YES ➡L6
L3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO YES	YES
	b	IF YES OR YES BIZARRE: do you currently believe these things?	NO YES	YES ➡L6
L4	a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO YES	YES
	b	IF YES OR YES BIZARRE: do you currently believe these things?	NO YES	YES ➡L6
L5	a	Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION, ETC.	NO YES	YES
	b	IF YES OR YES BIZARRE: do they currently consider your beliefs strange?	NO YES	YES
L6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING: IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO YES	YES
	b	IF YES OR YES BIZARRE TO L6a: have you heard these things in the past month? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO YES	YES ➡L8b

Appendix B M.I.N.I

L7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES
CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b IF YES: have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

L8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

L9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

L10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

L11 a ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L7a CODED YES OR YES BIZARRE AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT OR RECURRENT)

OR

MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED YES?

NO YES
➔L13

IF NO TO L11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO L13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM L1a TO L7a) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO L12 AND MOVE TO L13

NO YES

**MOOD DISORDER WITH
PSYCHOTIC FEATURES**

LIFETIME

L12 a ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED YES OR YES BIZARRE AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)

OR

MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED YES?

NO YES

**MOOD DISORDER WITH
PSYCHOTIC FEATURES**

CURRENT

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO L13 AND L14 AND MOVE TO THE NEXT MODULE.

L13 ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L6b, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « b » QUESTIONS FROM L1b TO L10b, CODED **YES** (RATHER THAN **YES BIZARRE**)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO	YES
<i>PSYCHOTIC DISORDER CURRENT</i>	

L14 IS **L13** CODED **YES**

OR

ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L6a, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « a » QUESTIONS FROM L1a TO L7a, CODED **YES** (RATHER THAN **YES BIZARRE**)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO	YES
<i>PSYCHOTIC DISORDER LIFETIME</i>	

M. ANOREXIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

M1 a	How tall are you?	<input type="text"/> ft <input type="text"/> in.
		<input type="text"/> cm.
b.	What was your lowest weight in the past 3 months?	<input type="text"/> lbs.
		<input type="text"/> kgs.
c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	➡ NO YES

In the past 3 months:

M2	In spite of this low weight, have you tried not to gain weight?	➡ NO YES
M3	Have you intensely feared gaining weight or becoming fat, even though you were underweight?	➡ NO YES
M4 a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO YES
b	Has your body weight or shape greatly influenced how you felt about yourself?	NO YES
c	Have you thought that your current low body weight was normal or excessive?	NO YES
M5	ARE 1 OR MORE ITEMS FROM M4 CODED YES?	➡ NO YES
M6	FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	➡ NO YES

FOR WOMEN: ARE M5 AND M6 CODED YES?

FOR MEN: IS M5 CODED YES?

NO YES
ANOREXIA NERVOSA
CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M²

Height/Weight		4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
ft/in															
lbs.		81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm		145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs		37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight		5'11	6'0	6'1	6'2	6'3
ft/in						
lbs.		125	129	132	136	140
cm		180	183	185	188	191
kgs		57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m² for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

N. BULIMIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

N1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ NO YES
N2	In the last 3 months, did you have eating binges as often as twice a week?	➡ NO YES
N3	During these binges, did you feel that your eating was out of control?	➡ NO YES
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ NO YES
N5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO YES
N6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO YES ↓ Skip to N8
N7	Do these binges occur only when you are under (____lbs./kgs.)? <small>INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.</small>	NO YES
N8	IS N5 CODED YES AND IS EITHER N6 OR N7 CODED NO?	<div style="border: 1px solid black; padding: 5px; text-align: center;"> NO YES BULIMIA NERVOSA CURRENT </div>
	IS N7 CODED YES?	<div style="border: 1px solid black; padding: 5px; text-align: center;"> NO YES ANOREXIA NERVOSA <i>Binge Eating/Purging Type</i> CURRENT </div>

O. GENERALIZED ANXIETY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

O1	a	Have you worried excessively or been anxious about several things over the past 6 months?	➡ NO	YES
	b	Are these worries present most days?	➡ NO	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	➡ YES
O2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	➡ NO	YES
O3		FOR THE FOLLOWING, CODE NO IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning waking or sleeping excessively)?	NO	YES
		ARE 3 OR MORE O3 ANSWERS CODED YES?	<div style="border: 1px solid black; padding: 10px; text-align: center;"> NO YES GENERALIZED ANXIETY DISORDER CURRENT </div>	

P. ANTISOCIAL PERSONALITY DISORDER (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.)

P1	Before you were 15 years old, did you:		
a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES
	➡	NO	YES
	ARE 2 OR MORE P1 ANSWERS CODED YES?		

DO NOT CODE YES TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

P2	Since you were 15 years old, have you:		
a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE 3 OR MORE P2 QUESTIONS CODED YES?

NO	YES
ANTISOCIAL PERSONALITY DISORDER LIFETIME	

THIS CONCLUDES THE INTERVIEW

REFERENCES

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonara LI, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC. Reliability and Validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. *European Psychiatry*. 1997; 12:232-241.

Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan K, Janavs J, Dunbar G. The MINI International Neuropsychiatric Interview (M.I.N.I.) A Short Diagnostic Structured Interview: Reliability and Validity According to the CIDI. *European Psychiatry*. 1997; 12: 224-231.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G: The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. *J. Clin Psychiatry*, 1998;59(suppl 20):22-33.

Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D: DSM-III-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (M.I.N.I.). Concordance and causes for discordance with the CIDI. *European Psychiatry*. 1998; 13:26-34.

Translations

Afrikaans

Arabic

Bengali

Braille (English)

Brazilian Portuguese

Bulgarian

Chinese

Czech

Danish

Dutch/Flemish

English

Estonian

Farsi/Persian

Finnish

French

German

Greek

Gujarati

Hebrew

Hindi

Hungarian

Icelandic

Italian

Japanese

Kannada

Korean

Latvian

Lithuanian

Malayalam

Marathi

Norwegian

Polish

Portuguese

Punjabi

Romanian

Russian

Serbian

Setswana

Slovenian

Spanish

Swedish

Tamil

Telugu

M.I.N.I. 5.0.0 (July 1, 2006)

M.I.N.I. 4.4 or earlier versions

R. Emsley

P. Amorim

L.G., Hranov

P. Bech

E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere

D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan,

E. Knapp, M. Sheehan

M. Heikkinen, M. Lijeström, O. Tuominen

Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine

I. v. Denffer, M. Ackenheil, R. Dietz-Bauer

S. Beratis

J. Zohar, Y. Sasson

I. Bitter, J. Balazs

I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano,

Y. Lecrubier, P. Donda, E. Weiller

V. Janavs, J. Janavs, I. Nagobads

G. Pedersen, S. Blomhoff

M. Masiak, E. Jasiak

P. Amorim

I. Timotijevic

L. Ferrando, J. Bobes-Garcia, J. Gilbert-Rahola, Y. Lecrubier

M. Waern, S. Andersch, M. Humble

M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0

and M.I.N.I. Screen 5.0:

W. Maartens

O. Osman, E. Al-Radi

H. Banerjee, A. Banerjee

P. Amorim

L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu,

C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng.

P. Zvlosky

P. Bech, T. Schütze

I. Van Vliet, H. Leroy, H. van Megan

D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan,

M. Sheehan

J. Shlik, A. Aluoja, E. Khil

K. Khooshabi, A. Zomorodi

M. Heikkinen, M. Lijeström, O. Tuominen

Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta

G. Stotz, R. Dietz-Bauer, M. Ackenheil

T. Calligas, S. Beratis

M. Patel, B. Patel, Organon

R. Barda, I. Levinson, A. Aviv

C. Mittal, K. Batra, S. Gambhir, Organon

I. Bitter, J. Balazs

J.G. Stefansson

L. Conti, A. Rossi, P. Donda

T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima,

J. Shinoda, K. Tanaka, Y. Okajima

Organon

K.S. Oh and Korean Academy of Anxiety Disorders

V. Janavs, J. Janavs

A. Bacevicius

Organon

Organon

K.A. Leiknes, U. Malt, E. Malt, S. Leganger

M. Masiak, E. Jasiak

P. Amorim, T. Guterres

A. Gahunia, S. Gambhir

O. Driga

A. Bystritsky, E. Selivra, M. Bystritsky, L. Shumyak,

M. Klisinska.

I. Timotijevic

K. Ketlogetswe

M. Kocmur, M. Kocmur

L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes-

Garcia, O. Soto, L. Franco, G. Heinze, C. Santana,

R. Hidalgo

C. Allgulander, H. Agren M. Waern, A. Brimse,

M. Humble.

Organon

Organon

Appendix B M.I.N.I

Thai

P. Kittirattanapaiboon, S. Mahatnirunkul, P. Udomrat,
P. Silpakit, M. Khamwongpin, S. Srikosai.
T. Örnek, A. Keskiner, A.Engeler
S. Gambhir

Turkish T. Örnek, A. Keskiner, I. Vahip
Urdu

A validation study of this instrument was made possible, in part, by grants from SmithKline Beecham and the European Commission.
The authors are grateful to Dr. Pauline Powers for her advice on the modules on Anorexia Nervosa and Bulimia.

Appendix C - Amphetamine Withdrawal Questionnaire (AWQ)

Amphetamine Withdrawal Questionnaire

Initials:

Date:

Visit:

DURING THE PAST 24 HOURS:

CIRCLE ONE ANSWER PER QUESTION

	0	1	2	3	4
1. Have you been craving amphetamine or methamphetamine?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
2. Have you felt sad?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
3. Have you lost interest in things or no longer take pleasure in them?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
4. Have you felt anxious?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
5. Have you felt as if your movements are slow?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
6. Have you felt agitated?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
7. Have you felt tired?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
8. Has your appetite increased, or have you eaten too much?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
9. Have you had any vivid or unpleasant dreams	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>
10. Have you been craving for sleep or sleeping too much?	<i>Not at all</i>	<i>Very little</i>	<i>A little</i>	<i>Quite a lot</i>	<i>Very much</i>

1. Hyperarousal subscale score (items1 + 6 + 9) :
2. Anxiety subscale score (items3 + 4 + 5) :
3. Reversed vegetative subscale score (items7 + 8 + 10) :
4. Total AWQ score (all three subscale scores + item 2) :

Appendix D - Brief Substance Craving Scale (BSCS)

Brief Substance Craving Scale

Initials:

Date:

Visit:

Please answer the following questions with regard to your craving for methamphetamine.

1. The INTENSITY of my craving, that is, how much I desired this drug in the past 24 hours was:

- | | |
|--------------|----------------------------|
| None at all | <input type="checkbox"/> 0 |
| Slight | <input type="checkbox"/> 1 |
| Moderate | <input type="checkbox"/> 2 |
| Considerable | <input type="checkbox"/> 3 |
| Extreme | <input type="checkbox"/> 4 |

2. The FREQUENCY of my craving, that is, how often I desired this drug in the past 24 hours was:

- | | |
|-------------------|----------------------------|
| N e v e r | <input type="checkbox"/> 0 |
| Almost never | <input type="checkbox"/> 1 |
| Several times | <input type="checkbox"/> 2 |
| Regularly | <input type="checkbox"/> 3 |
| Almost constantly | <input type="checkbox"/> 4 |

3. The LENGTH of time I spent in craving this drug during the past 24 hours was:

- | | |
|---------------|----------------------------|
| None at all | <input type="checkbox"/> 0 |
| Very short | <input type="checkbox"/> 1 |
| Short | <input type="checkbox"/> 2 |
| Somewhat long | <input type="checkbox"/> 3 |
| Very long | <input type="checkbox"/> 4 |

Appendix E - Abnormal Involuntary Movement Scale (AIMS)

Abnormal Involuntary Movement Scales

Initials:

Date:

Visit:

Instructions: Complete examination procedure before making ratings.
Rate highest severity observed.

Code: 1 None
 2 Minimal, may be extreme normal
 3 Mild
 4 Moderate
 5 Severe

Facial and Oral Movements:

- | | | | | | | |
|----|---|---|---|---|---|---|
| 1. | Muscles of facial Expression (e.g., movement of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing) | 1 | 2 | 3 | 4 | 5 |
| 2. | Lips and Perioral Area (e.g., puckering, pouting, smacking) | 1 | 2 | 3 | 4 | 5 |
| 3. | Jaws (e.g. biting, clenching, chewing, mouth opening, lateral movement) | 1 | 2 | 3 | 4 | 5 |
| 4. | Tongue (Rate only increase in movement both in and out of mouth, NOT inability to sustain movement.) | 1 | 2 | 3 | 4 | 5 |

Extremity Movements:

- | | | | | | | |
|----|---|---|---|---|---|---|
| 5. | Upper (arms, wrists, hands, fingers). Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic). | 1 | 2 | 3 | 4 | 5 |
| 6. | Lower (legs, knees, ankles, toes). (E.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.) | 1 | 2 | 3 | 4 | 5 |

Appendix E - AIMS

Trunk Movements:

7. Neck, shoulders, hips (e.g., rocking, twisting, squirming, pelvic gyrations)

1 2 3 4 5

Global judgments

8. Severity of abnormal movements:

1. None, normal
2. Minimal
3. Mild
4. Moderate
5. Severe

9. Incapacitation due to abnormal movements:

1. None, normal
2. Minimal
3. Mild
4. Moderate
5. Severe

10. Patient's awareness of abnormal movements (Rate only patient's report)

1. No awareness
2. Aware, no distress
3. Aware, mild distress
4. Aware, moderate distress
5. Aware, severe distress

Dental Status:

11. Current problems with teeth and/or dentures

1. No
2. Yes

12. Does patient usually wear dentures?

1. No
2. Yes

Appendix F- Barnes Akathasia Scale (BARS)

Barnes Akathisia Rating Scale (BARS)

Initials:

Date:

Visit:

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

- 0** Normal, occasional fidgety movements of the limbs
- 1** Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or “walking on the spot” when standing, but movements present for less than half the time observed
- 2** Observed phenomena, as described in (1) above, which are present for at least half the observation period
- 3** Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

- 0** Absence of inner restlessness
- 1** Non-specific sense of inner restlessness
- 2** The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
- 3** Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness:

- 0** No distress
- 1** Mild
- 2** Moderate
- 3** Severe

Global Clinical Assessment of Akathisia:

- 0** *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
- 1** *Questionable.* Non-specific inner tension and fidgety movements
- 2** *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.
- 3** *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
- 4** *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
- 5** *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

Appendix G - Simpson Angus Scale (SAS)

SIMPSON-ANGUS EXTRAPYRAMIDAL SIDE EFFECTS SCALE

Initials:

Date:

Visit:

The exam should be conducted in a room where the subject can walk a sufficient distance to allow him/her to get into a natural rhythm (e.g. 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this score should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items 3, 4, 5, and 6. It is not rated separately and is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.

1. **Gait:** The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture; all form the basis for an overall score for this item. This is rated as follows:

0 Normal

1 Diminution in swing while the patient is walking

2 Marked diminution in swing with obvious rigidity in the arm

3 Stiff gait with arms held rigidly before the abdomen

4 Stooped shuffling gait with propulsion and retropulsion

2. **Arm Dropping:** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:

0 Normal, free fall with loud slap and rebound

1 Fall slowed slightly with less audible contact and little rebound

2 Fall slowed, no rebound

3 Marked slowing, no slap at all

4 Arms fall as though against resistance; as though through glue

3. **Shoulder Shaking:** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one

hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost a frozen shoulder

4. **Elbow Rigidity:** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost a frozen elbow

5. **Wrist Rigidity or Fixation of Position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation:

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost frozen

6. **Leg Pendulousness:** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:

0 The legs swing freely

1 Slight diminution in the swing of the legs

2 Moderate resistance to swing

Appendix G

3 Marked resistance and damping of swing

4 Complete absence of swing

7. **Head Dropping:** The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table.

0 The head falls completely with a good thump as it hits the table

1 Slight slowing in fall, mainly noted by lack of slap as head meets the table

2 Moderate slowing in the fall quite noticeable to the eye

3 Head falls stiffly and slowly

4 Head does not reach the examining table

8. **Glabella Tap:** Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:

0 0-5 blinks

1 6-10 blinks

2 11-15 blinks

3 16-20 blinks

4 21 and more blinks

9. **Tremor:** Patient is observed walking into examining room and is then reexamined for this item:

0 Normal

1 Mild finger tremor, obvious to sight and touch

2 Tremor of hand or arm occurring spasmodically

3 Persistent tremor of one or more limbs

4 Whole body tremor

10. **Salivation:** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:

0 Normal

Appendix G

- 1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised
- 2 When excess salivation is present and might occasionally result in difficulty speaking
- 3 Speaking with difficulty because of excess salivation
- 4 Frank drooling

Appendix H - Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Initial:

Date:

Visit:

- | | | |
|---|--|---|
| A | I feel tense or 'wound up': | |
| | Most of the time | 3 |
| | A lot of the time | 2 |
| | From time to time, occasionally | 1 |
| | Not at all | 0 |
| D | I still enjoy the things I used to enjoy: | |
| | Definitely as much | 0 |
| | Not quite so much | 1 |
| | Only a little | 2 |
| | Hardly at all | 3 |
| A | I get a sort of frightened feeling as if something awful is about to happen: | |
| | Very definitely and quite badly | 3 |
| | Yes, but not too badly | 2 |
| | A little, but it doesn't worry me | 1 |
| | Not at all | 0 |
| D | I can laugh and see the funny side of things: | |
| | As much as I always could | 0 |
| | Not quite so much now | 1 |
| | Definitely not so much now | 2 |
| | Not at all | 3 |
| A | Worrying thoughts go through my mind: | |
| | A great deal of the time | 3 |
| | A lot of the time | 2 |
| | From time to time, but not too often | 1 |
| | Only occasionally | 0 |
| D | I feel cheerful: | |
| | Not at all | 3 |
| | Not often | 2 |
| | Sometimes | 1 |
| | Most of the time | 0 |
| A | I can sit at ease and feel relaxed: | |
| | Definitely | 0 |
| | Usually | 1 |
| | Not Often | 2 |
| | Not at all | 3 |

Appendix H

D	I feel as if I am slowed down:	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	I get a sort of frightened feeling like 'butterflies' in the stomach:	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3
D	I have lost interest in my appearance:	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0
A	I feel restless as I have to be on the move:	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	I look forward with enjoyment to things:	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	I get sudden feelings of panic:	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	I can enjoy a good book or radio or TV program:	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Appendix I - Positive and Negative Symptoms Scale(PANSS)

Positive and Negative Symptoms Scale

Initials:

Date:

Visit:

Positive Symptoms

P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7

Negative Symptoms

N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7

Appendix I - PANSS

General Psychopathology

G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

Appendix J - Clinical Global Impressions Scale (CGI-S)

Clinical Global Impressions Scale

Initials:

Date:

Visit:

SEVERITY OF ILLNESS

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- | | |
|---------------------------------------|----------------------------|
| Normal, not at all ill | <input type="checkbox"/> 1 |
| Borderline mentally ill | <input type="checkbox"/> 2 |
| Mildly ill | <input type="checkbox"/> 3 |
| Moderately ill | <input type="checkbox"/> 4 |
| Markedly ill | <input type="checkbox"/> 5 |
| Severely ill | <input type="checkbox"/> 6 |
| Among the most extremely ill patients | <input type="checkbox"/> 7 |

Appendix K- Approval Letter

Appendix K- Approval Letter from Ethical Committee/ Government Authorities



JAWATANKUASA ETIKA PERUBATAN PUSAT PERUBATAN UNIVERSITI MALAYA

ALAMAT: LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEFON: 03-79494422 FAKSIMILI: 03-79545682

MEDICAL ETHICS COMMITTEE COMPOSITION, UNIVERSITY MALAYA MEDICAL CENTRE



Date: 20th FEBUARI 2008

Member (Title and Name)	Occupation (Designation)	Male/Female (M/F)	Tick (✓) if present when above items were reviewed
Chairperson: Prof. Looi Lai Meng	Representative Dean/Director	Female	✓
Secretary: Puan Norehan Ahmad	Science Officer, PTj UH Diagnostics	Female	✓
Members: 1. Prof. Jamiyah Hassan	Deputy Director	Female	
2. Prof. Mohd Hussain Habil	Head of Department of Psychological Medicine	Male	✓
3. Prof. Tan Chong Tin	Representative Head Of Department Of Medicine	Male	✓
4. Prof. Madya. Dr. Gong Ngie Hee	Representative Head of Department of Pharmacology	Male	✓
5. Prof. Madya. Dr. Colin Ng Leong Liong	Representative Head of Department of Surgery	Male	✓
6. Prof. Madya. Grace Xavier	Lecturer, Faculty of Law	Female	✓
7. Tuan Haji Amrahi Buang	Senior Manager, PTj Farmasi	Male	✓
8. YBhg. Datin Aminah Pit Abdul Rahman	Public Representative	Female	✓
9. Madam Ong Eng Lee	Public Representative	Female	✓

Comments: The MEC of University Malaya Medical Centre is operating according to ICH GCP guideline and the Declaration of Helsinki. Members no. 6, 7, 8 & 9 are representatives from Faculty of Law in the University of Malaya and the public, respectively. They are independent of the hospital or trial site.


PROF. LOOI LAI MENG
Chairman
Medical Ethics Committee

Appendix K- Approval Letter

 JAWATANKUASA ETIKA PERUBATAN PUSAT PERUBATAN UNIVERSITI MALAYA ALAMAT: LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA TELEFON: 03-79494422 FAKSIMILI: 03-79545682	
NAME OF ETHICS COMMITTEE/IRB: Medical Ethics Committee, University Malaysia Medical Centre ADDRESS: LEMBAH PANTAI 59100 KUALA LUMPUR PROTOCOL NO: AHS001 TITLE: A Randomized Placebo-Controlled Trial Of The Safety And Efficacy Of Aripiprazole In The Treatment Of Amphetamine Type Stimulant Dependence PRINCIPAL INVESTIGATOR: Prof. Madya. Dr. Ahmad Hatim Sulaiman TELEPHONE: _____ KOMTEL: _____	ETHICS COMMITTEE/IRB REFERENCE NUMBER: 637.3 SPONSOR: _____
The following item <input checked="" type="checkbox"/> have been received and reviewed in connection with the above study to be conducted by the above investigator.	
<input checked="" type="checkbox"/> Borang Permohonan Penyelidikan <input checked="" type="checkbox"/> Study Protocol <input checked="" type="checkbox"/> Subject Information Sheet <input checked="" type="checkbox"/> Investigator Brochure <input checked="" type="checkbox"/> Subject's Legally Acceptable Representative's Informed Consent <input type="checkbox"/> Questionnaire <input checked="" type="checkbox"/> Investigator (s) CV's (Prof. Madya. Dr. Ahmad Hatim Sulaiman)	Ver date: 27 Dec 07 Ver date: Ver date: Ver date: Ver date:
and have been <input checked="" type="checkbox"/>	
<input checked="" type="checkbox"/> Approved <input type="checkbox"/> Conditionally approved (identify item and specify modification below or in accompanying letter) <input type="checkbox"/> Rejected (identify item and specify reasons below or in accompanying letter)	
Comments: i. Investigator is required to follow instructions, guidelines and requirements of the Medical Ethics Committee. ii. Investigator is required to report any protocol deviations/violations through the Clinical Investigation Centre and provide annual/closure reports to the Medical Ethics Committee.	
Date of approval: 20 th February 2008	
s.k Ketua Jabatan Perubatan Psikologi Timbalan Dekan (Penyelidikan) Fakulti Perubatan, Universiti Malaysia Setiausaha Jawatankuasa Penyelidikan Pusat Perubatan Fakulti Perubatan, Universiti Malaysia	 PROF. LOOI LAI MENG Chairman Medical Ethics Committee

Appendix K- Approval Letter



JAWATANKUASA ETIKA PERUBATAN PUSAT PERUBATAN UNIVERSITI MALAYA

ALAMAT: LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEFON: 03-79494422 FAKSIMIL: 03-79545682

NAME OF ETHICS COMMITTEE/IRB: Medical Ethics Committee, University Malaya Medical Centre		ETHICS COMMITTEE/IRB REFERENCE NUMBER: 673.42
ADDRESS: LEMBAH PANTAI 59100 KUALA LUMPUR		
PROTOCOL NO: AHS001		
TITLE: A Randomized Placebo Controlled Trial Of The Safety And Efficacy Of Aripiprazole In The Treatment Of Amphetamine Type Stimulant Dependence		
PRINCIPAL INVESTIGATOR: Prof. Madya Dr. Ahmad Hatim Sulaiman		SPONSOR:
TELEPHONE:	KOMTEL:	

The following item [✓] have been received and reviewed in connection with the above study to be conducted by the above investigator.

- [] Borang Permohonan Pindaan Penyelidikan
- [] Protocol Amendment
- [] Investigator Brochure
- [✓] Advertisement Of Clinical Trial In Local Newspaper (English, Malay)
- [] Questionnaire
- [] Investigator(s) CV's (if applicable)

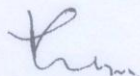
Ver date:
Ver date:
Ver date:
Ver date:
Ver date:

and have been [✓]

- [✓] Approved
- [] Conditionally approved (identify item and specify modification below or in accompanying letter)
- [] Rejected (identify item and specify reasons below or in accompanying letter)

Comments:

Date of approval: 27th OGOS 2008


PROF. LOOI LAI MENG
 Chairman
 Medical Ethics Committee

Appendix K- Approval Letter



KEMENTERIAN KESIHATAN MALAYSIA
Ministry of Health Malaysia
BAHAGIAN PERKHIDMATAN FARMASI
Pharmaceutical Services Division
Lot 36, Jalan Universiti, 46350 Petaling Jaya, Selangor, Malaysia

Your Ref/ Ruj. Tuan :

Our Ref/ Ruj. Kami : Bil (3) dlm KKM-55/205/001/04

Date / Tarikh : 22 Oktober 2008



Prof Madya Dr Ahmad Hatim Sulaiman
Jabatan Perubatan Psikologi
Fakulti Perubatan Universiti Malaya
50603 Kuala Lumpur.

Tuan,

**Iklan "Clinical Study Volunteers" di dalam Suratkhbar Tempatan untuk kajian:
Randomized Controlled Trial of the Safety and Efficacy of Aripiprazole in the
Treatment of Amphetamine Type Stimulant Dependence**

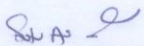
Adalah saya merujuk kepada perkara di atas dan surat daripada pihak tuan yang bertarikh 13 Oktober 2008.

2. Sukacitanya dimaklumkan bahawa Lembaga Iklan Ubat meluluskan iklan tersebut dengan pindaan pada tajuk iklan seperti di lampiran. Tajuk yang diputuskan oleh Lembaga Iklan Ubat ialah: "**Kajian Percubaan Rawatan Untuk Penagih: Ecstasy, Ice, Shabu, Yaaba, Pil Kuda**" bagi bahasa Malaysia dan "**Clinical Study for Treatment of Ecstasy, Ice, Yaaba, Pil Kuda Abuse Dependence**" bagi bahasa Inggeris.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,


(SITI AIDA BINTI ABDULLAH)
Setiausaha
Lembaga Iklan Ubat
Kementerian Kesihatan Malaysia

aud

Alamat Surat Menyurat / Correspondence Address
Beg Berkunci No. 924, Pejabat Pos Jalan Sultan, 46790 Petaling Jaya, Selangor, Malaysia.
Tel : 603-7968 2200 Fax : 603-7968 2222 <http://www.pharmacy.gov.my>

Appendix K- Approval Letter



PUSAT SERENTI PAPAR (PUSPA)
AGensi ANTIDADAH KEBANGSAAN MALAYSIA
KEMENTERIAN KESELAMATAN DALAM NEGERI,
BEG BERKUNCI NO. 7,
BT. 30, JALAN PAPAR - BEAUFORT,
89609 PAPAR, SABAH, MALAYSIA.



Tel : 088-912487 / 088-912893
Fax : 088-915786
E-mail : puspasbh@tm.net.my

Ruj. Tuan :
Ruj. Kami : **ADK.PSP.30/16/ (36)**
Tarikh : **19 FEBUARI 2008**

Dr.Ahmad Hatim Sulaiman
Pensyarah Kanan
Jabatan Perubatan Psikologi
Pusat Perubatan Universiti Malaya
Jalan Universiti
59100 Kuala Lumpur

Tuan,

KEBENARAN MENJALANKAN KAJIAN "ASSOCIATION BETWEEN GENETIC POLYMORPHISM WITH DRUGS ADDICTION TO STIMULANTS" DI PUSAT SERENTI PAPAR (PUSPA) SABAH

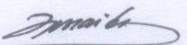
Dengan segala hormatnya izinkan saya merujuk kepada surat Ibu Pejabat Agensi Antidadah Kebangsaan(AADK) bil.ADK 20/4/4/1 () bertarikh 5 Disember 2007 dan surat tuan bertarikh 13 Febuari 2008.

2. Sukacita dimaklumkan bahawa Pusat Serenti Papar (PUSPA) **tiada halangan** kepada tuan untuk menjalankan kajian tersebut ke atas penghuni kami.
3. Jika terdapat sebarang masalah dengan perkara ini sila berhubung dengan pegawai kami, **En.Zunaidie bin M.Taib** di talian 088-912487 (samb.211).

Sekian,terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,


(ZUNAIIDIE BIN M.TAIB)
b.p.Komandan
Pusat Serenti Papar
SABAH

s.k
Y.Bhg.Dato' KP
TKP(O)

**MEMBASMI DADAH ADALAH TANGGUNGJAWAB KITA BERSAMA
MARILAH BERTINDAK SEGERA**

Appendix K- Approval Letter



JABATAN PENJARA MALAYSIA
KEMENTERIAN DALAM NEGERI
PENJARA PUSAT
PETI SURAT 11020
88811 KOTA KINABALU

Telefon 088-236777
Fax 088-270470
Kawat "PENJARA" Koat Kinabalu



Rujukan Kami : JP/SBH(KK)/Am/102/1 Klt.3 (13)
Tarikh : 18 November 2009

Jabatan Perubatan Psikologi
Fakulti Perubatan
Universiti Malaya
50603 Kuala Lumpur
Malaysia

(u.p: Prof.Madya Dr.Ahmad Hatim Sulaiman)

Tuan,

**PERMOHONAN UNTUK MENYAMBUNG PENGUMPULAN DATA UNTUK KAJIAN
"ASSOCIATION BETWEEN GENETIC POLYMORPHISM WITH DRUG ADDICTION TO
STIMULATION" DI PENJARA PUSAT KOTA KINABALU**

Saya dengan segala hormatnya merujuk kepada surat tuan bertarikh 12 Oktober 2009 berhubung perkara di atas.

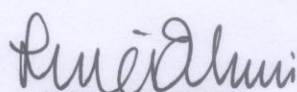
2. Sukacita dimaklumkan bahawa lawatan kajian "Association Between Genetic Polymorphism With drug addiction To Stimulant" adalah **diluluskan** oleh pihak Ibu Pejabat Penjara Malaysia melalui surat rujukan iaitu JP/LTH/Rd/102/3 Klt.31 (59) bertarikh 02 September 2009.

3. Dimaklumkan juga bahawa penyelia untuk lawatan kajian ini ialah Ketua Inspektor Rajesh bin Juri bagi membantu tuan semasa kajian dibuat.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,


(SURIA BIN IDRIS)
Pengarah
Penjara Pusat
Kota Kinabalu.

18 NOV 2009
Telah difaks pada

Appendix K- Approval Letter



PEJABAT PENGARAH HOSPITAL
HOSPITAL QUEEN ELIZABETH
KARUNG BERKUNCI NO. 2029,
88586 KOTA KINABALU,
SABAH, MALAYSIA
Tel: 088-517555 Faks: 088-211999/318605



Ruj. Tuan :

Ruj. Kami : (45)dIm.PHQEH(SB)171/430/487/1 Jld.2

Tarikh : 19 Jun 2008.

Jabatan Kesihatan Negeri Sabah
Tingkat 3, Rumah Persekutuan
Jalan Mat Salleh
Kota Kinabalu.
(u.p.: Timbalan Pengarah Kesihatan (Perubatan))

Tuan,

**MEMOHON MEMPEROLEHI SAMPEL 'BUCCAL SWABS' DARI
PESAKIT-PESAKIT LUAR HOSPITAL QUEEN ELIZABETH, SABAH
BAGI TUJUAN KAJIAN**

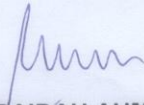
Dengan hormatnya perkara di atas adalah dirujuk.

2. Bersama-sama ini disertakan surat permohonan daripada Universiti Malaya dikemukakan untuk kelulusan daripada pihak tuan selanjutnya.

Sekian, terima kasih.

“ BERKHIDMAT UNTUK NEGARA “

Saya yang menurut perintah,



(DR. ZURAIDAH AHMAD BABJI)
Pengarah
Hospital Queen Elizabeth
Kota Kinabalu.


→ s.k: Professor Madya Dr. Ahmad Hatim Sulaiman
Pakar Perunding Psikiatri/Pensyarah
Jabatan Perubatan Psikologi
Fakulti Perubatan, Universiti Malaya
50603 Kuala Lumpur.

DRZAB/ls

“ MEMBANTERAS DADAH – APAKAH SUMBANGAN ANDA? ”

Appendix L - Research Grant

**UNIVERSITI
MALAYA**
KUALA LUMPUR
Producing Leaders Since 1905



IPPP/UPDiT/Geran (PJP)/FS151/2007C

26 Oktober 2007

Ahmad Hatim Sulaiman
Jabatan Perubatan Psikologi
Fakulti Perubatan
Universiti Malaya

Tuan/Puan,

**KATA LALUAN (PASSWORD) BAGI PERUNTUKAN PENYELIDIKAN JANGKA PENDEK (PJP)
AGIHAN 3 - 2007 DI BAWAH GERAN KHAS UNIVERSITI PENYELIDIKAN 2007, UM**

Dengan hormatnya perkara di atas adalah dirujuk.

Seperti yang telah dimaklumkan kepada tuan/puan jumlah peruntukan yang telah diluluskan ialah sebanyak **RM 50000** dengan butiran seperti berikut :-

No. Akaun :	FS151/2007C
Tajuk :	Association between genetic polymorphisms with drug addiction to stimulants
Tempoh :	01 Oktober 2007 – 30 September 2008
Katalaluan :	dUQxVtRB

* Tuan/Puan boleh menyemak status kewangan akaun ini melalui laman web
<http://www.ippp.um.edu.my/eFinance>





PECAHAN	RM
Alat Khusus & Aksesori	18000
Bekalan	20300
Perjalanan & Sara hidup	3900
Elaun & Gaji pekerja	7800
JUMLAH	50000

Segala urusan perbelanjaan (pembelian & pembayaran) dan semakan akaun mestilah menggunakan sistem kewangan baru melalui laman web : <http://www.ippp.um.edu.my/eFinance>. Manual penggunaan sistem boleh didapati di dalam laman web tersebut. Sebarang pertanyaan mengenai sistem kewangan ini boleh diajukan kepada En. Mohd Rezalman bin Eiderudin (03- 7967 6952).



Kesemua tuntutan perbelanjaan hendaklah dikemukakan kepada Unit Penyelidikan DiTaja (UPDiT), Institut Pengurusan Penyelidikan & Perundingan (IPPP), Universiti Malaya melalui Penyalin dan Ketua Jabatan / Bahagian untuk diproses. Segala tuntutan mestilah sampai ke Unit ini tidak lewat dari tarikh akhir akaun ini. Tuntutan selepas tarikh ini tidak akan dilayan.

Tuan/Puan perlu kemukakan laporan kepada Unit seperti berikut;

1. Laporan Status Kemajuan Projek (6 bulan)	: 30 April 2008
2. Laporan Akhir Projek	: 30 September 2008


MS ISO 9001:2000 REG. NO. AR 2760

Unit Penyelidikan DiTaja (UPDiT)
Institut Pengurusan Penyelidikan dan Perundingan
A205, Bangunan IPS, Universiti Malaya, 50603 Kuala Lumpur
Tel: (603) 7967 4522/4653/4652 • Faks: (603) 7967 4648
email: ketua_upd_ippp@um.edu.my • <http://www.ippp.um.edu.my>



338



Appendix M - Advertisement in Newspapers

Raya,
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mengeluarkan iklan tersebut pada minggu terdekat.
Sila pastikan tempahan awal untuk mengelakkan kekecewaan.

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ADAKAH ANDA ATAU AHLI KELUARGA ANDA:

- ✓ Mempunyai masalah menyalahgunakan dadah "Ecstasy, Ice, Shaboo, Yabaa, Pil Kuda"?
- ✓ Ingin mendapatkan pertolongan untuk menyelesaikan masalah tersebut
- ✓ Sanggup mendapat rawatan berterusan selama 3 bulan

**KAJIAN PERCUBAAN RAWATAN
UNTUK PENAGIH:
"ECSTASY, ICE, SHABOO,
YABAA, PIL KUDA"**

Di Unit Kajian Perubatan Psikologi, Pusat Perubatan Universiti Malaya, kami terlibat dalam kajian terbaru untuk merawat penagihan dadah. (Ketua penyelidik: Prof.Madya Dr.Ahmad Hatim Sulaiman)

Adakah anda berminat untuk secara SUKARELA menyertai kajian ini selama 3 bulan dengan menggunakan ubat baru yang berbeza dengan rawatan yang sedia ada. Rawatan adalah PERCUMA!

Sekiranya anda atau ahli keluarga anda ada masalah ketagihan dadah seperti di atas dan inginkan maklumat lanjut, sila hubungi kami di talian:

Tel: 03-7957 0995 (Kam Lee)/ 03-7960 4367 (Aina)
Fax: 03-7957 1058

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Appendix N - Article write up in Newspaper : Berita Harian and China Press

canal **BERITA MINGGU** **bmdua** **3**
Ahad 6 September 2009

Penagih dadah sintetik sering hilang pertimbangan

PENGAMBILAN dadah perangsang dalam tempoh panjang akan merosakkan fizikal dan mental kerana ia adalah campuran bahan beracun, kata Perunding Psikiatri Pusat Perubatan Universiti Malaya (PPUM), Prof Madya Dr Ahmad Hatim Sulaiman.

Beliau berkata, selain kerosakan gigi, gusi, sistem penghadaman dan hati, kesan paling teruk ialah kerosakan saraf otak yang boleh menyebabkan penagih menjadi gila.

"Nasihat saya jangan sekali-mencuba. Pengedar mendakwa ia tidak menyebabkan ketagihan tetapi saya mahu tegaskan dadah sintetik memang menyebabkan ketagihan. Sekali mencuba, mereka akan terus ketagih."

"Mereka yang mengambil dadah ini akan mengalami simptom seperti mendengar suara, percaya adanya ancam yang mendorong mereka bertindak ganas termasuk membunuh."

"Selepas mengambil dadah itu, reaksi penagih bergantung kepada keadaannya ketika itu. Jika takut, dia akan berasa sangat takut seperti mendakwa nampak hantu dan jika dalam keadaan marah, mereka akan bertindak agresif," katanya.

Beliau berkata, Jabatan Perubatan Psikologi Fakulti Perubatan PPUM ada menyediakan rawatan untuk penagih dadah sintetik sejak setahun lalu dan mencatatkan kejayaan memberangsangkan.

"Kami membekalkan ubat dan rawatan percuma selama tiga bulan untuk penagih dadah sintetik kerana masih pada peringkat kajian."

Mereka dirawat dengan ubat dan psikoterapi. Dalam kes ini, seramai 40 penagih tegar dadah sintetik terbabit dan boleh dikatakan lebih separuh daripada mereka sudah sembuh sepenuhnya.

"Bagi kes teruk, penagih akan ditempatkan di wad untuk seminggu atau dua minggu kemudian dibenarkan keluar selepas mendapati keadaan mereka semakin stabil. Bagi sebulan atau dua bulan, rawatan susulan dilakukan seminggu sekali dan seterusnya bergantung kepada keadaan mereka."

"Ada yang datang secara sukarela selepas membaca iklan dalam akhbar dan ada juga keluarga yang datang merujuk anggota keluarga mereka ke sini. Peratus kejayaan begitu memberangsangkan," katanya.

Katanya, penagih atau keluarga yang berminat boleh menghubungi beliau di talian 03-79604367 untuk maklumat lanjut.

Sementara itu, Presiden Persatuan Pengasih Malaysia (Pengasih), Mohd Yunus Pathi, berkata penagih yang mengambil dadah sintetik membabitkan campuran bahan kimia cenderung hilang pertimbangan dan bertindak agresif hingga membahayakan orang lain.

Mengulas kejadian menyayat hati yang menimpa Mohd Adam Azrai, Mohd Yunus, berkata dadah sintetik seperti syabu mampu membuatkan penagih berdepan kemurungan teruk dan cepat marah.

"Pengambilan ganja dalam tempoh lama juga memberikan kesan sama. Dalam kejadian itu, penagih mungkin nampak kanak-kanak berkenaan sebagai objek yang mengancam dan membuatkan dia bertindak menikam mangsa."

"Sebenarnya banyak lagi kes seumpama itu yang berlaku tetapi tidak dilaporkan. Jenayah dilakukan penagih tegar seperti rogol, sumbang mahram, pukul sehingga membabitkan pembunuhan tidak dilaporkan keluarga."

"Mereka mungkin malu untuk berdepan tindakan polis dan mahkamah tetapi sikap itu menyebabkan tragedi berlaku. Malah ada kes suami isteri yang sudah bercerai tetapi masih tinggal serumah semata-mata untuk menjaga status kemasyarakatan mereka," katanya.

Mohd Yunus menggesa keluarga supaya segera melaporkan kehadiran penagih tegar di kalangan mereka kepada pihak berkuasa untuk mengelakkan kejadian yang menimpa Mohd Adam Azrai tidak berulang lagi.

"Hasil 18 tahun membabitkan diri mengendalikan kaedah pemulihan, saya dapati keluarga tidak mengizinkan laporan dibuat mengenai anggota keluarga mereka yang menagih dadah. Saya minta mereka buang rasa malu, sebaliknya laporkan segera kepada badan seperti Agensi Anti Dadah Kebangsaan (AADK) demi keselamatan keluarga."

"Penagih seperti ini tidak boleh mengawal kemarahan mereka atau panas baran. Perkara biasa kepada orang lain dilihat besar oleh penagih dadah sintetik dan mendorong mereka bertindak ganas," katanya.

Penagih seperti ini panas baran. Perkara biasa kepada orang lain dilihat besar oleh penagih dadah sintetik dan mendorong mereka bertindak ganas"

Mohd Yunus Pathi
Presiden Pengasih

Selepas mengambil dadah, reaksi penagih bergantung kepada keadaannya. Jika takut, dia berasa sangat takut seperti mendakwa nampak hantu dan jika dalam keadaan marah, mereka akan bertindak agresif, katanya.



新型毒祸延烧

第一篇

▲与传统毒品比较，新型毒品在价钱上较便宜、方便得多，因此受年轻人欢迎。

▲隐形吸毒者，他们与一般人想像中的吸毒者不同，多数有正当职业。

隐形吸毒者是新隐忧

一直以来，毒品就是国家头号敌人，宣扬毒品坏处的反毒运动从来没有停止过，但吸毒人口不但没有减少，反而增加。

再朗朗上口的反毒口号，还是无法阻遏“毒势力”入侵。

新型毒品，造就了越来越多隐形吸毒者出现，这些人不是不知道吸毒是不良示范、错误行为，但为了逃避现实、挑战权威、爱面子、受不了诱惑、好玩……甘于沉沦毒海。

有一名吸毒者有感而发地说，不到进棺材那一天，都无法确定自己还会不会再吸毒。

很多人吸毒后，都会后悔，但毒瘾一来，又无法抑制，想尽办法拿料（买毒），一旦清醒后，又再后悔，身陷这样一个恶性循环，什么意志力都被消蚀磨光了。

在戒毒所，这样的瘾君子占了大多数，他们有悔意，但无法凭一己之力戒毒，最后才会求助戒毒所，这也是戒毒所收留吸毒者的起条件：你必须要有悔意、想戒毒。

无论如何，戒毒所的吸毒者只是一小撮，外头还有数以万计，浮游在社会的吸毒者，有的一早被家人、社会遗弃，只能躲在阴暗角落挣扎求存、流落街头。

隐形吸毒者数目上升

惟，新型毒品的出现，造成隐形吸毒者（drug users）的数目上升。

所谓隐形，指外人不容易察觉他们染毒的吸毒者，这些人可能是知识分子、拥有正当职业、有家庭孩子的正常人，或者是偶尔想放松心情、减压的上班族、大专生，甚至外劳，隐形吸毒者与我们想中的吸毒者不相同。

一般人对瘾君子刻板印象是不务正业、游手好闲、东偷西抢，但现代隐形吸毒者大多有正当职业，他们可能是公务员、小贩、行政人员、销售员等等，看似正常的外表、正当职业，掩饰了他们是吸毒者的事实。

新型毒品能够穿透职业、阶级、身分，只有发生意外，或是健康亮红灯时，这些隐形吸毒者身分才会曝光。

▲阿末哈旬医生：冰毒吸

渴望戒毒却戒不掉

阿飞（化名）就是一个例子。他的家人、雇主不知道他染毒，他也照常工作，事实上，他是K他命上瘾者，每天都花上50令吉来解瘾，毒龄约两年。

他自小不爱读书，初中三辍学后，转投社会大学，在一家修车厂做学徒，学徒生涯苦似海，每天最早到工厂的是他，最迟离开的也是他，挨了好几年，总算出师，每月有稳定收入。

年轻人，最流行泡夜店，他也跟著大伙儿上夜店喝酒、跳舞、结识女性朋友，周末一到，大伙儿相约在夜店作乐，玩乐至天亮。

他说，从小父母就告诫他不可吸毒，但他还是禁不住朋友诱惑，以为试一试无妨。

第一次尝毒，没有快感，他几乎睡死了，完全不晓得发生什么事，心有不甘的他，再试第二次，才尝到快感，“总之就是特别开心、舒服和爱讲话。”接下来，他累积了很多次吸毒经验。

只有堕落到底

即使沾毒，他内心深处还是有戒毒念头，每次只敢少量服用，中间还停停吸了好几天，不过总是无法成功戒掉，他这时才明白已

内外观察吸毒症状

如何察觉隐形吸毒者？马大医院精神顾问兼讲师阿末哈旬医生指出，他们大多数出现以下征状：

先是毫无原因旷课、旷工，学校成绩或是工作表现突然变差，无心学习、工作。

经济状况突然变差，常常钱不够用、家里不时发生财物失窃，或者突然频繁向人借钱，亲人、朋友无一例外。

▼年轻人好玩、权威……容易

成为毒品禁闭，他懊悔、愧疚得更多，最后他为止。

有这种想法的，抱着这种想法，有人来救，最后只

他坦言，朋友尿片、有人骨瘦、朋友离奇坠楼死

眼看毒友们没的，深感悔恨，不了。

在成熟的外表，更不懂自己接下来。

他渴望戒毒，会不会去戒毒中

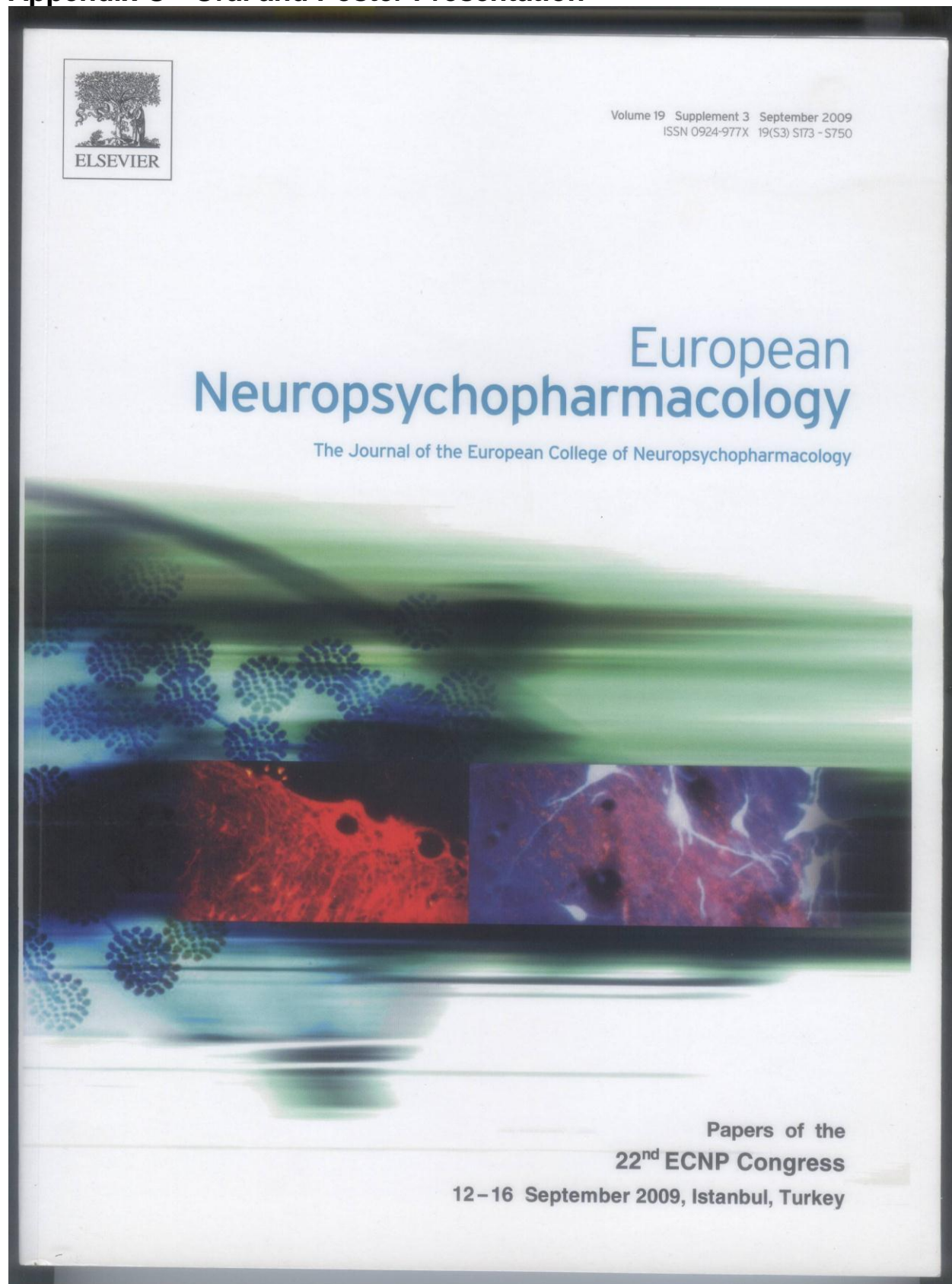
毒的事曝光。

到底如何才能围只余死寂。

气暴躁、沉默等外形方面，急裂、老化，牙齿两眼无神，这些为明显。

他提醒说，若鼻孔四周是否留生理症状包括

Appendix O - Oral and Poster Presentation



S654

P.6.c Addiction - Drugs (clinical)

- [2] Heinz et al (2005) Arch Gen Psych 62:57-64
 [3] Williams et al (2008) Eur Neuropsychopharmacology 2007;18(S4):536

P.6.c.008 Pharmacogenetic modulation of neurocognitive deficits in MDMA users: The role of catechol-O-methyltransferase, serotonin transporter SERT and 5HT2A polymorphisms

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Purpose: MDMA (3,4-methylenedioxymethamphetamine, ecstasy) use has been related with important negative effects on cognition, including learning, memory and executive functions. A recent longitudinal study from our laboratory demonstrated considerable stability in deficits on verbal fluency, working memory and processing speed in ecstasy users [1]. Cognitive impairments associated with ecstasy use have been linked to drug induced alterations in the serotonergic function, although MDMA also impacts dopamine and noradrenalin systems strongly involved in higher-order cognition [2]. A number of functional polymorphisms on dopamine and serotonin genes have been recently associated with neurocognition, and may thus interact with MDMA-induced neuropsychological deficits [3]. The purpose of this study was to investigate how functional polymorphisms in dopamine (COMT val^{108/158}met, rs165599 and rs2097603) and serotonin (5-HTTLPR and 5HT2A His452Tyr and T102C) genes modulate performance on the cognitive domains previously associated with lifetime MDMA use and its persistent effects.

Methods: Thirty-seven ecstasy polydrug users and 57 non ecstasy users were evaluated in: Semantic Fluency; Verbal Working Memory (Letter Number Sequencing); Visual Working Memory (Corsi Blocks); Verbal Episodic Memory (California Verbal Learning Test-CVLT); Visual Episodic Memory (Rey-Osterrieth Complex Figure Test-ROCF); Planning (Tower of London-ToL); and Attention/Processing Speed (Symbol Digit Modalities Test-SDMT). All subjects were genotyped for 5-HTTLPR, 5HT2A His452Tyr and T102C, COMT val^{108/158}met, rs165599 and rs2097603 polymorphisms. Genotyping was performed by PCR (5-HTTLPR/5HT2A) and TaqMan polymerase assay (COMT).

Results: Dopamine genes: A significant group \times COMT val^{108/158}met genotype interaction for performance on ROCFT immediate recall ($p=0.049$) and SDMT ($p=0.02$) was found. A group \times rs165599 genotype interaction was observed for performance on ROCFT immediate ($p=0.019$), and delayed recall ($p=0.05$) and on ToL ($p=0.05$). Finally a significant group \times rs2097603 genotype interaction was observed for performance on CVLT learning ($p=0.004$).

Serotonin genes: A significant group \times 5HT2A His452Tyr genotype interaction was found for performance on Letter Number Sequencing ($p=0.005$). In addition, we found main effects of genotype for CVLT indices of learning ($p=0.01$) and immediate recall ($p=0.02$); ROCFT immediate ($p=0.04$), and delayed recall ($p=0.04$; and ToL ($p=0.01$). Similarly, for the 5HT2A T102C genotype, main effects of genotype for semantic fluency ($p=0.03$), CVLT learning ($p=0.01$) and Corsi blocks ($p=0.01$) were observed. No effects of genotype or group \times genotype interaction were found for 5HTTLPR.

Conclusions: Our results indicate an interaction between the COMT polymorphisms and MDMA use on the visual memory, planning and controlled attention speed deficits of MDMA users. These findings are consistent with evidences linking COMT genes with executive function and prefrontal functioning, implicating COMT activity in ongoing regulation of attentional control. With regard to serotonin genes, we found a significant interaction between MDMA use and the 5HT2A His452Tyr polymorphism specifically for verbal working memory, with Tyr allele carriers showing poorer performance. In addition, results indicated that 5HT2A polymorphisms were associated with poorer performance across tests of visual episodic memory, semantic fluency, verbal learning and visual working memory, irrespective of MDMA use. These findings suggest a functional role of these polymorphisms in brain systems endorsing memory and executive functions which are usually impaired in MDMA users.

References

- [1] de Sola Llopis S., Mígueluez-Pan M., Peña-Casanova J., Poudevida S., Farré M., Pacifici R., Böhm P., Abanades S., Verdejo García A., Langohr K., Zuccaro P., de la Torre R., 2008 Cognitive performance in recreational ecstasy polydrug users: a two-year follow-up study. *Journal of Psychopharmacology* 22, 498-510.
 [2] de la Torre R., Farré M., Roset P.N., Pizarro N., Abanades S., Segura M., Segura J., Camí J., 2004 Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. *Therapeutic Drug Monitoring* 26, 137-144.
 [3] Reneman L., Schilt T., de Win M.M., Booij J., Schmand B., van den B.W., Bakker O., 2006 Memory function and serotonin transporter promoter gene polymorphism in ecstasy (MDMA) users. *Journal of Psychopharmacology* 20, 389-399.

P.6.c.009 Psychiatric co-morbidity among patients with amphetamine and methamphetamine dependence in Malaysia

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Introduction: An estimate of 30 million people in the world used amphetamine and methamphetamine compared with 15 million who used opiates and 13 million who used cocaine [1]. The past decade has seen a marked increase in the popularity of stimulant abuse, particularly methamphetamine, within East Asia and the Pacific region [2]. Although there has been a marked increase in amphetamine and methamphetamine dependence, the psychiatric sequelae of amphetamine and methamphetamine dependence have not been well characterized. In substance dependence disorders other than amphetamine and methamphetamine dependence, increased psychiatric co-morbidity is associated with poorer treatment outcome [3]. The high level of amphetamine and methamphetamine use has been associated with an increased prevalence in functional psychosis.

The objective of this study was to examine the prevalence of psychiatric co-morbidity among amphetamine and methamphetamine dependence patients. Factors associated with drug induce psychosis among amphetamine and methamphetamine dependence patients were also explored.

Methods: The study was approved by the University of Malaya Medical Ethics. This was a cross-sectional study. The data were obtained from patients who were admitted to a drug rehabilitation centre in Malaysia. All patients who consented for the study

were interviewed. A structured face-to-face interview was used to collect data for this study. The prevalence rates of lifetime and current psychotic symptoms and other psychiatric diagnosis were determined by using Mini-International Neuropsychiatric Interview. The data on drug use, demographic profile, and symptoms of psychosis in the past year were also obtained from the patients. Information on other associated factors related to substance dependence was also collected. Data of 106 patients (all male) were obtained from those who fulfilled the DSM IV criteria for amphetamine and methamphetamine dependence. Buccal swab was also obtained from the patients to determine the genetic polymorphism.

Results: Among the 106 patients, 12.3% had major depressive episodes in their lifetime and 6.6% have attempted suicide. 13.2% had manic episode and 6.6% fulfill the DSM IV criteria for schizophrenia. 2.8% of the patients had panic disorder, 1.9% had generalised anxiety disorder, 5.7% had social phobia and 0.9% had obsessive compulsive disorder. 33.0% were found to abuse alcohol and 40.6% fulfill the DSM IV criteria for drug induce psychosis. 36.8% have antisocial personality disorder. Polysubstance abuse (OR 5.7, 95%CI: 2.1, 18.2) especially cannabis and alcohol, antisocial personality disorder (OR 6.6, 95%CI: 2.7, 16.4) and psychiatric co-morbidity (OR 22.2, 95%CI: 6.7, 99.6) especially schizophrenia and bipolar affective disorders were associated with more risk of developing psychotic symptoms. Genetic polymorphism results will be reported in another study.

Conclusion: These findings suggest that amphetamine and methamphetamine-dependent patients are at greater risk to experience psychiatric co-morbidity. Drug induce psychosis is the most common psychiatric co-morbidity among amphetamine and methamphetamine dependent patients. Further studies are warranted to examine the aetiology of this co-morbidity.

References

- [1] United Nations Office on Drugs and Crime. 2004 World Drug Report; Vol 1
- [2] Farrell M, Marsden J, Ali R, Ling W. Methamphetamine: drug use and psychoses becomes a major public health issue in the Asia Pacific region. *Addiction*. 2002 Jul;97(7):771-2.
- [3] Cacciola J, Alterman A, Rutherford M. The relationship of psychiatric co-morbidity to treatment outcomes in methadone maintained patients. *Drug and alcohol dependence*. 2001 Feb; 61 (3): 271-280.

P6.c.010 Pharmacodynamic response patterns to ketamine, zolpidem, and diazepam in abuse liability studies

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Many of the new drugs being developed for CNS related disorders require evaluation for abuse potential [1,2], since they often have novel mechanisms of action and do not always fall into the traditional classifications of CNS acting compounds. The methodology to assess abuse potential has required adjustment in the types of comparators utilized. Hence, drugs such as ketamine, zolpidem, and diazepam are more frequently being used to distinguish positive effects of tests drugs compared to placebo.

Successful qualification was based on greater than placebo peak drug liking and higher overall preference for multiple active drugs. A total of 113 males and females, age 18 to 65 years old

were randomized into two double-blind crossover trials in which they received single doses of placebo, ketamine (100 mg), and zolpidem (20 mg) or diazepam (20 mg). The pharmacodynamic measures were selected for their sensitivity to positive, negative, and perceptual drug effects and were administered using the Kendle Early Stage proprietary software. Data obtained at 0.5, 1, 2, 4, and 23 hours post-dose were analyzed using repeated measures ANOVA including administration time as repeated effect, treatment as fixed effect, and subject as random effect.

Table 1. Multiple comparisons

Measure	Ketamine vs Diazepam	Ketamine vs Zolpidem	Diazepam vs Zolpidem
ARCI-LSD	0.68**	0.26	0.43
ARCI-PCAG	2.54***	2.51***	0.32
Alertness	15.52***	18.36***	2.84
Detachment	12.83***	6.60*	6.23
Floating	9.79**	6.23*	3.56
Hallucinations	12.30***	2.32	14.62***
Overall Drug Liking	1.97	11.13*	9.16

*P < 0.05, **P < 0.01, ***P < 0.001.


Seventy-six (77%) subjects were qualified based on the ability to provide meaningful ratings of their drug experiences as reflected by significant treatment (P < 0.05) and time from dosing (P < 0.05) differences between placebo and comparators. Addiction Research Center Inventory (ARCI) results showed that compared to diazepam, ketamine was associated with significantly increased euphoria (F = 13.72, P < 0.001) and compared to diazepam and zolpidem, it was associated with fewer dysphoric or somatic complaints (F = 62.28, P < 0.001). Subjective visual analog scales results showed that ketamine was associated with intact levels of alertness (F = 37.2, P < 0.001), increased feelings of detachment (F = 36.76, P < 0.001) and increased floating sensations (F = 44.23, P < 0.001) compared to diazepam and zolpidem. Hallucinations were reported for ketamine and zolpidem, but not for diazepam (F = 20.15, P < 0.001). At 23 hours post-dose, subjects reported significant overall drug liking (F = 21.93, P < 0.001) and desire to take the active drugs again compared to placebo (F = 33.86, P < 0.001) however, zolpidem was associated with significantly lower overall drug liking than ketamine. Significant post-hoc mean differences are included in Table 1. The study was adequately powered to detect treatment differences.

In conclusion, qualified subjects can perceptively apply their polydrug use experience to identify differences and similarities between drugs that they used in the past. Distinct response patterns on measures designed to examine subjective effects were present for different drugs. Thus, the evaluation of the overall pattern of responding on various measures of subjective drug effects is essential for the assessment of abuse potential.

This study is sponsored by Kendle Early Stage - Toronto and Sanofi-Aventis US, Inc.

References

- [1] Schoedel, K.A., Sellers, E.M., 2008 Assessing abuse liability during drug development: changing standards and expectations. *Clinical Pharmacology and Therapeutics*, 83, 622-626.
- [2] Chen, L., Tsong, Y., 2007 Design and analysis for drug abuse potential studies: Issues and strategies for implementing a crossover design. *DIA Journal*, 41, 481-489.



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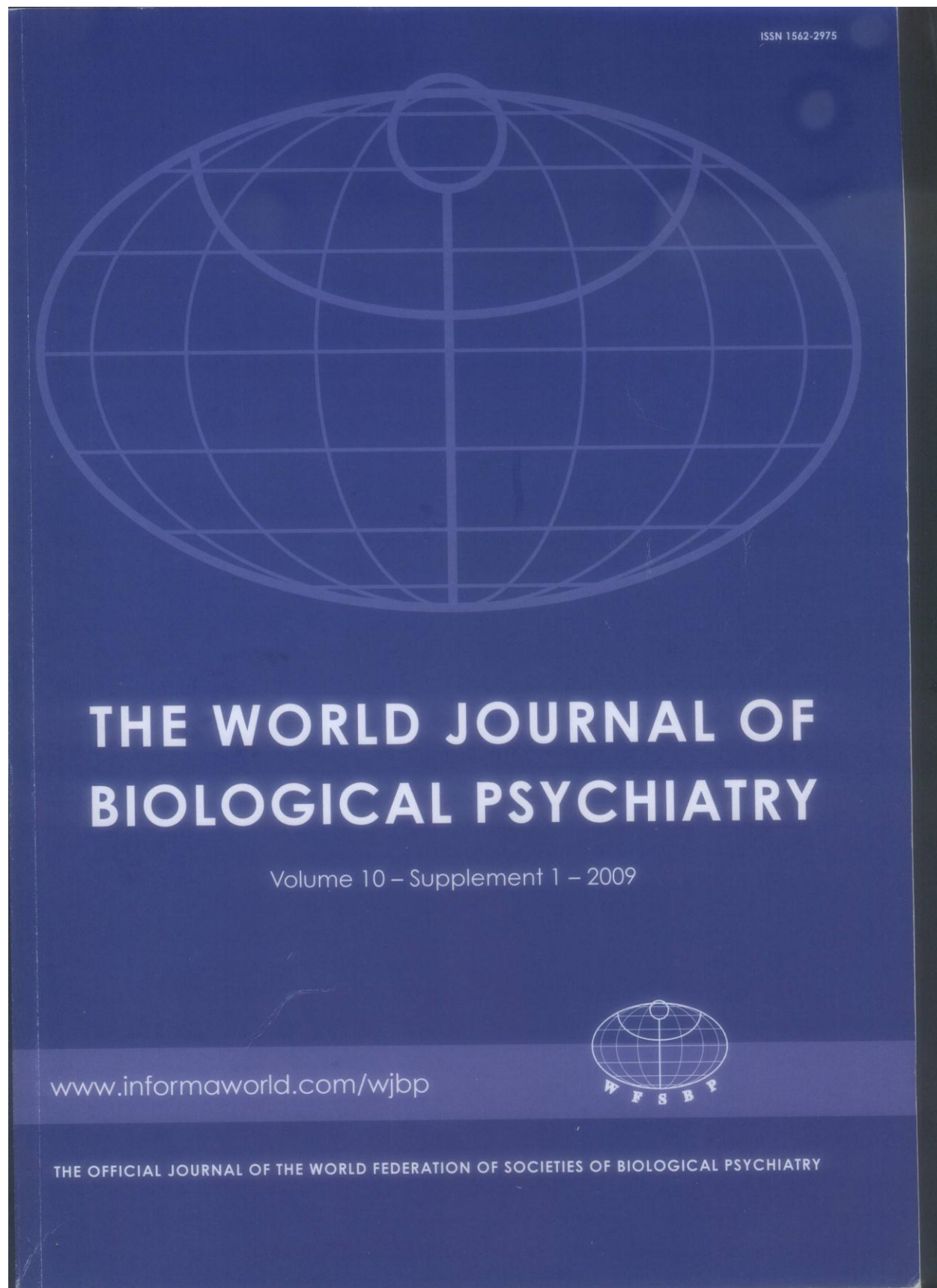
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P-48-020

Risk factors of aripiprazole treatment discontinuation in Japanese schizophrenia patients

Yoshiteru Takekita

Kansai Medical University, Neuropsychiatry, Osaka, Japan

Masaki Kato, Aran Tajika, Shiho Sakai, Ayumi Suzuki, Azusa Suwa, Kei-ichiro Nishida, Masataka Wakano, Gaku Okugawa, Toshihiko Kinoshita

Objectives: Aripiprazole is second generation antipsychotics used widely all over the world. The aim of this study was to determine factors associated with aripiprazole treatment discontinuation in Japanese schizophrenia patients.

Methods: This was a retrospective cohort analysis of schizophrenia patients consecutively admitted to the Department of Neuropsychiatry at Kansai Medical University between August 1, 2006, and November 30, 2008, and treated with aripiprazole. Diagnoses were identified using DSM-IV codes. Kaplan-Meier survival curves were generated for the time-to-discontinuation data, and differences among treatment groups were compared using log-rank tests at an alpha level lower than 0.05 level of significance. All analyses were conducted using SPSS Version 15.0.

Results: 210 patients included in this study were divided into three groups by the aripiprazole dose (low dose group: < 6 mg/day, $N = 65$, moderate dose group: $7-17$ mg/day, $N = 52$, high dose group: > 18 mg/day, $N = 65$). Strong significance was detected between high dose group and low dose group with higher risk of discontinuation in low dose group ($p < 0.0001$). Significant difference could not be seen among following three strategies: (I) immediate aripiprazole initiation with simultaneous immediate discontinuation of other antipsychotics; (II) immediate aripiprazole initiation while tapering off other antipsychotics; (III) titrating aripiprazole upwards while tapering off other antipsychotics in 127 patients switched from other antipsychotics to aripiprazole.

Conclusions: In Japanese patients, treatment with sufficient dose can avoid discontinuation compared to low dose. On the other hand, switching strategies were not related the development of discontinuation. The findings from this study should be interpreted conservatively because of its non-randomized observational design.

P-49

Psychopharmacology III

P-49-001

Prevalence of drug induce psychosis among amphetamine and methamphetamine dependence patients

Ahmad Hatim Sulaiman

University Malaya, Dept of Psychological Medicine, Kuala Lumpur, Malaysia

Mas Ayu Said, Mohd Hussain Habil

Objectives: Psychosis associated with stimulant use is an increasing problem, but there is little research evidence about the nature of the problem. The present study was aimed at exploring the prevalence of psychosis and factors associated with drug induce psychosis among amphetamine and methamphetamine dependence patients.

Methods: This was a cross-sectional study. The data were obtained from patients who were admitted to a drug rehabilitation centre in Malaysia. All patients who consented for the study were interviewed. A structured face-to-face interview was used to assess drug use, demographics, and symptoms of psychosis in the past year and other associated factors. The prevalence rates of lifetime and current psychotic symptoms and other psychiatric diagnosis were determined by using Mini-International Neuropsychiatric Interview. Data of 106 patients (all male) were obtained from those who fulfilled the DSM IV criteria for amphetamine and methamphetamine dependence. Buccal swab was also obtained from the patients to determine the genetic polymorphism.

Results: 36.8% had experienced clinically significant psychotic symptoms in the past year. Polysubstance abuse (OR 5.7, 95% CI: 2.1, 18.2) especially cannabis and alcohol, antisocial personality disorder (OR 6.6, 95% CI: 2.7, 16.4) and psychiatric co-morbidity (OR 22.2, 95% CI: 6.7, 99.6) especially schizophrenia and bipolar affective disorders were associated with more risk of developing psychotic symptoms. Other factors were duration of drug dependence ($p < 0.05$) and amount of money spend to buy the drugs ($p < 0.05$). Genetic polymorphism results will be reported in another study.

Conclusions: Dependent amphetamine and methamphetamine users are a particularly high-risk group for psychosis especially those with psychiatric co-morbidity, poly-substance abuse and antisocial personality disorder.

P-49-002

Safety and efficacy of aripiprazole in the treatment of amphetamine and methamphetamine induce psychosis: A preliminary results

Ahmad Hatim Sulaiman

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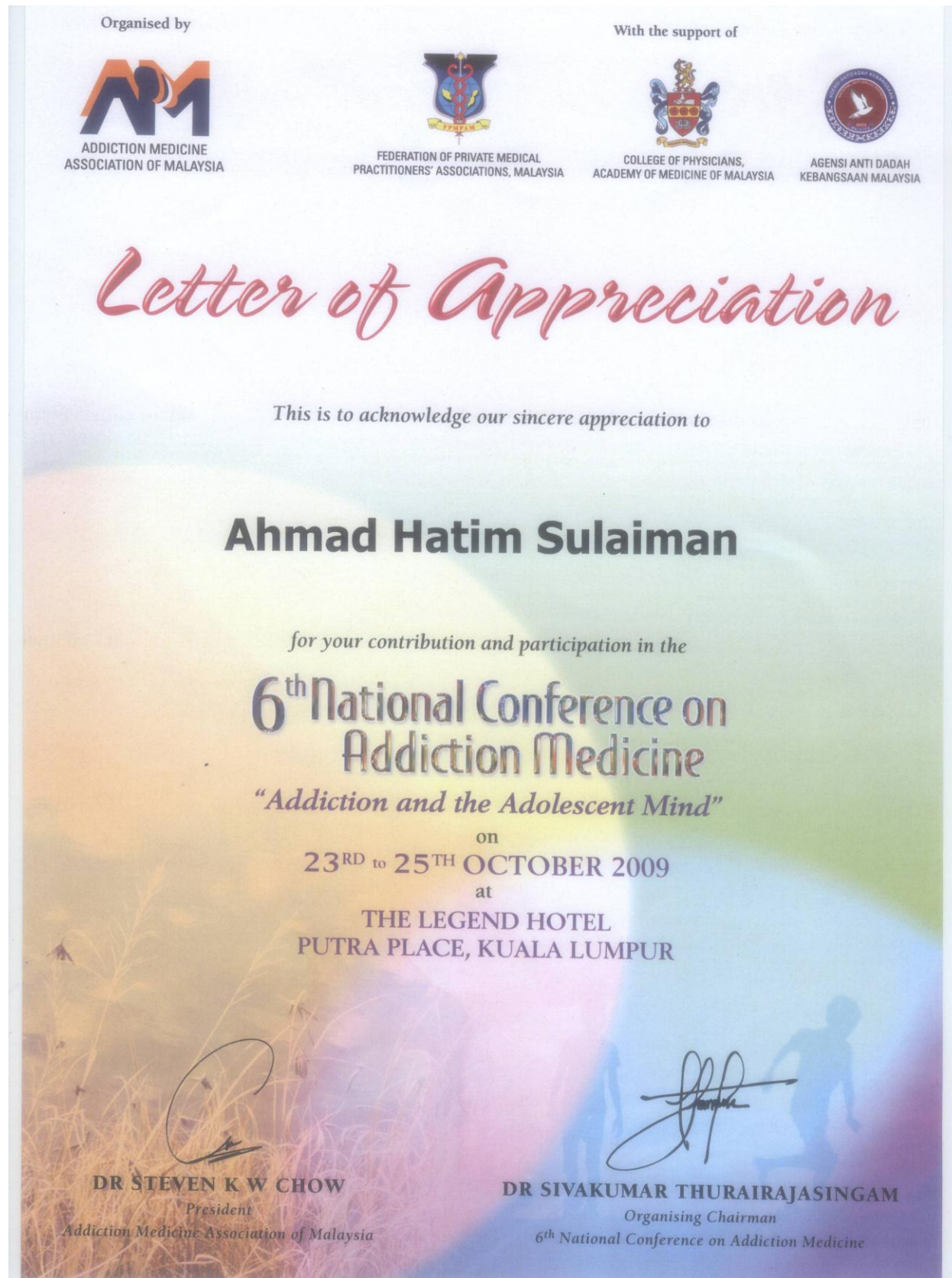
Mas Ayu Said, Mustafa Mohd, Mohd Hussain Habil

Objectives: To date there have been no reports on safety and efficacy of aripiprazole in amphetamine type stimulant (ATS) induce psychosis. The primary objective of the study is to determine the safety of Aripiprazole in treatment of ATS induce psychosis using the BARS, SAS, AIMS and adverse events (AE) monitoring as safety measures. The secondary objective is to determine the efficacy of Aripiprazole in the treatment of ATS induce psychosis using the PANSS and CGI scales as efficacy measures.

Methods: Open-label pilot study, approved by Ethics Committee involving 22 patients. Treatment duration was 14 days. Inclusion criteria were male or female, aged 18 – 60 year, current DSM-IV diagnosis of ATS dependence; urine must be positive for amphetamine and methamphetamine at time of screening; able to provide written informed consent and to comply with all study procedures; having psychotic symptoms with PANSS score of more than 60 and CGI score more than 3. Exclusion criteria were pregnant or breast-feeding women, any significant clinical disorders; individuals with any DSM-IV Axis I disorder not defined in the inclusion criteria. Patients were started on 10 mg of aripiprazole and dose can be titrated up or down depending on the patients' tolerability. No other antipsychotics were allowed. All patients were antipsychotic naive.

Results: Akathisia was the most common AE, however the overall BARS, SAS and AIMS score was not significant (all $p > 0.05$). No patients required dose adjustment or discontinued from the study due to AEs. Significant improvement was observed in PANSS and CGI Severity of Illness scores by day 7 (all $p < 0.05$), and was maintained throughout the study at day 14 (all $p < 0.05$).

Conclusions: Most patients tolerated aripiprazole therapy, with statistically and clinically significant improvement in psychotic symptoms by day 7. Aripiprazole is safe and effective for the treatment of ATS induce psychosis.









**PERSATUAN PERUBATAN MALAYSIA
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16 March 2010

Associate Prof Dr Ahmad Hatim Sulaiman
Dept of Psychological Medicine
Faculty of Medicine, University Malaya
50603 Kuala Lumpur

Dear Dr Dr Ahmad Hatim Sulaiman

~~A Seminar by Malaysian Medical Association Substance Abuse Committee 'Substance Abuse
Perils Issues and Solutions' on 25 April 2010 at Grand Seasons Hotel, Kuala Lumpur.~~

We are pleased to inform you that the above mentioned Seminar shall be organised by the Substance Abuse Committee, Malaysian Medical Association (MMA).

The Organising Committee would like to invite you to deliver the presentations as follows:-

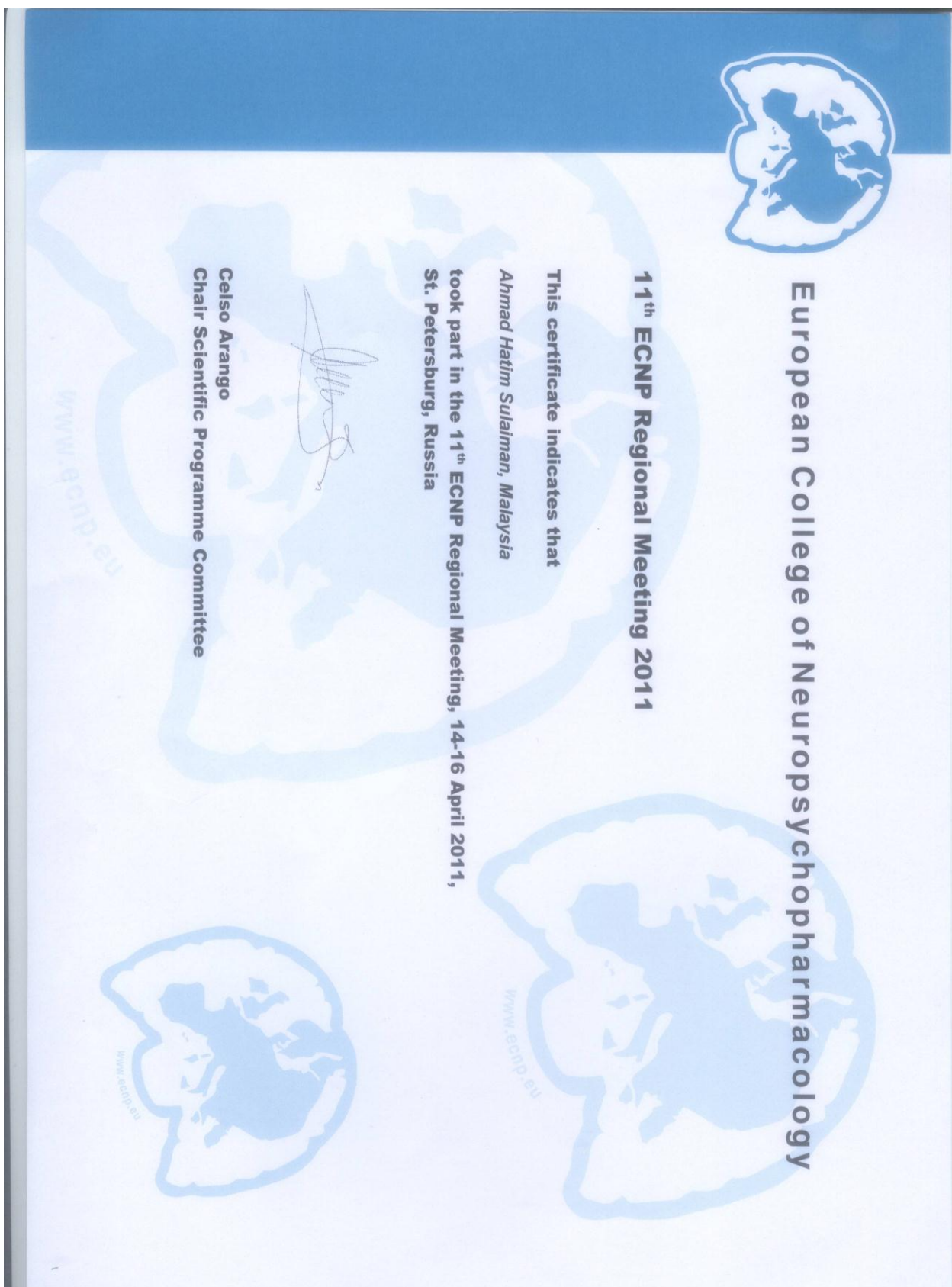
Date: 25 April 2010 (Sunday)
Time: 09.00 a.m. – 09.45 a.m.
Topic: The Scourge of Designer Drugs

A LCD projector and a laptop PC will be provided. For any additional requirements, please contact the MMA secretariat (Attention: Ms Hema). Kindly submit your power-point presentation material in hand out format and curriculum vitae (max one page) to the secretariat by e-mail to soem@mma.org.my by **10 April 2010.**

We look forward to meeting you and wish to thank you in advance for your cooperation in this matter.

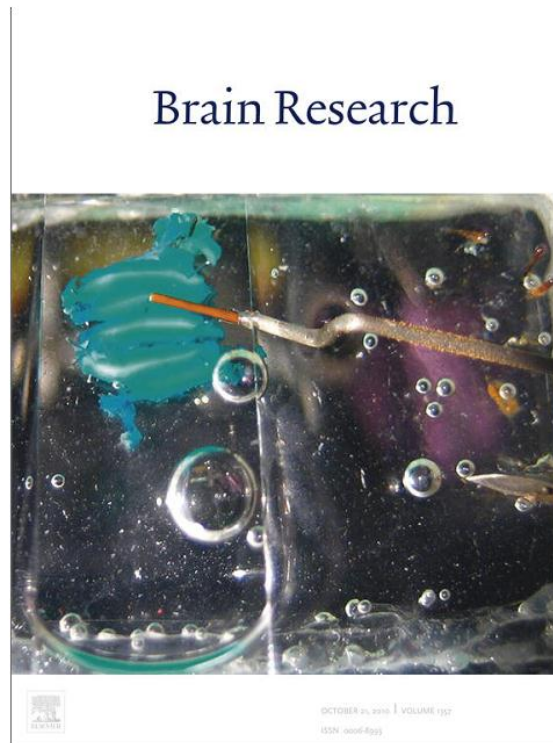
Thank you.
Yours faithfully,

DATO' DR N.K.S. THARMASEELAN
Honorary General Secretary
Malaysian Medical Association



Appendix P - Publications

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**BRAIN
RESEARCH**

Research Report

Association of brain-derived neurotrophic factor (Val66Met) genetic polymorphism with methamphetamine dependence in a Malaysian population

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ARTICLE INFO

Article history:
Accepted 17 August 2010
Available online 21 August 2010

Keywords:
Brain-derived neurotrophic factor
Methamphetamine dependence
Psychosis
Association study
Single nucleotide polymorphism

ABSTRACT

Methamphetamine is a highly addictive psychostimulant that has surged in popularity worldwide in the last decade. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, is widely expressed in the adult mammalian brain and plays an important role in the long-term survival, differentiation, and outgrowth of neurons. Previous studies suggested that the BDNF gene may be involved in the mechanisms underlying substance dependence. This study investigated the association of the BDNF gene Val66Met polymorphism with methamphetamine dependence and with psychosis in a Malaysian population with different ethnicities. The BDNF Val66Met polymorphism was genotyped by PCR-RFLP in 186 male methamphetamine-dependent subjects and in 154 male controls of four different ethnicities, namely, Malay, Chinese, Kadazan-Dusun, and Bajau. Our results showed that the distribution of the BDNF Val66Met genotype in Chinese subjects with methamphetamine dependence (OR=2.6, $p=0.015$) and methamphetamine psychosis (OR=0.2, $p=0.034$) were significant compared with controls. The frequency of the 66Val allele in methamphetamine-dependent subjects was higher than that in the control group, suggesting that the 66Val carriers are more susceptible to methamphetamine dependence. However, 66Val allele frequency in other ethnicities was not significantly different from the controls. The results of the study also showed that in the Chinese methamphetamine-dependent subjects, there was a difference in allele frequency when comparing those who developed psychosis and those who did not. Our findings suggest that the BDNF Val66Met polymorphism may contribute to methamphetamine dependence and psychosis in the Chinese population but not in other Malaysian ethnicities.

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Abbreviations: BDNF, brain-derived neurotrophic factor; DRD3, dopamine D3 receptor; Val, valine; Met, methionine; OR, odds ratio; CI, confidence interval; SD, standard deviation; N and n, number

¹ Fax: +60 3 79674791.

1. Introduction

Substance dependence remains a worldwide problem, and its negative impact on society is increasing. It is a chronic relapsing disorder in which compulsive drug-seeking and drug-taking behaviour persists despite serious negative consequences. The past decade has seen a remarkable increase in the popularity of methamphetamine within East Asia and the Pacific region. The United Nations Office on Drugs and Crime (UNODC) estimated that in 2005, 26 million people in the world used methamphetamine, 11 million used opiates, and 14 million used cocaine (United Nations Information Service (UNIS), 2005). It was also reported that 60% of methamphetamine users live in Asia. The impact of the spread of methamphetamine use, with its serious behavioural, medical, and psychiatric consequences, is being felt at the individual, familial, community, and societal levels, placing a tremendous strain on the medical, public health, and criminal justice systems. In Malaysia, the National Anti-Drug Agency (2008) identified 8870 addicts (January to August 2008), of whom 1126 were dependent on methamphetamine.

The Malaysian population is made up of various ethnic groups. Geographically, Malaysia is separated by the South China Sea into two regions, Peninsular Malaysia (also known as West Malaysia) and Malaysian Borneo (also known as East Malaysia), the latter being made up of two states, Sabah and Sarawak. According to the Yearbook of Statistics, Sabah (2001) from the Department of Statistics Malaysia (2000), the ethnic composition of West Malaysia and East Malaysia is very different, whereby the Malays (54% of the total Malaysian population; 11.5% of the Sabah population) and Chinese (25% of the total Malaysian population; 13.0% of the Sabah population) make up the majority ethnic group in West Malaysia, while in East Malaysia, the Kadazan-Dusun (2.5% of the total Malaysian population; 18.4% of the Sabah population) and Bajau (1.5% of the total Malaysian population; 13.5% of the Sabah population) make up the majority ethnic group. The subjects of this study were taken from a Rehabilitation Centre that is located in Sabah in which the majority of the population is of the Kadazan-Dusun and Bajau ethnic groups, besides the presence of other ethnic groups including the Chinese and Malays.

Brain-derived neurotrophic factor (BDNF), a member of the nerve growth factor-related family of neurotrophins, is widely expressed in the adult mammalian brain. Evidence indicates that BDNF may be involved in the mechanisms underlying substance abuse (Hofer et al., 1990). BDNF plays an important role in the neurodevelopment of dopaminergic (DA)-related systems. This protein interacts with the meso-limbic DA systems that are involved in the therapeutic response to substance abuse, and it subsequently promotes and maintains dopamine D3 receptor (DRD3) expression (Krebs et al., 2000). Methamphetamine is a drug that easily induces drug conditioning and elevated BDNF mRNA. BDNF expression has been found to increase acutely after drug abuse, leading to subsequent long-lasting elevation of DRD3 in the nucleus accumbens, which may facilitate response to drug-associated stimuli and finally induce addictive disorders (Le Foll et al., 2005). Genomic scans have demonstrated that the BDNF gene

is associated with vulnerability to drug abuse (Itoh et al., 2005). Recent pharmacogenomic studies have demonstrated the involvement of some single nucleotide polymorphisms in the response to drugs. The susceptible single nucleotide polymorphisms in some genes may contribute to addiction vulnerability in several ways, including changing the structure or function of specific proteins and altering the expression of brain circuit proteins during development or in adulthood. The altered brain circuits could change the responsiveness of the individual to initial drug exposure or to adaptations that occur in the brain after repeated drug exposure. However, environmental factors are also important and could affect addiction vulnerability by influencing the same neural circuits (Nestler, 2000).

Recent studies have demonstrated that the BDNF gene is associated with vulnerability to drug abuse (Itoh et al., 2005). Furthermore, Flanagan et al. (2006) reported that BDNF has been implicated in the behavioural response to psychomotor stimulants and that it potentiates neurotransmitters, which are strongly linked to addiction. They suggested that this gene is a logical candidate gene for the study of addiction. Data derived from animal studies have demonstrated that BDNF modulates dopaminergic and serotonergic functions that are strongly linked to substance abuse (Dluzen et al., 1999).

BDNF, located on chromosome 11p13, contains a common and functional single nucleotide polymorphism, rs6265 (Val66Met), at codon 66. This G196A polymorphism results in a valine (Val) to methionine (Met) substitution in the prodomain, which affects intracellular trafficking and activity-dependent secretion of BDNF (Li et al., 2005). A previous study reported that the valine (196G) allele is more commonly methamphetamine dependent and suggested that the GG genotype is a risk factor for substance abuse, related to late onset of substance abuse (Cheng et al., 2005).

According to Haile et al. (2009), this BDNF polymorphism is not only linked to methamphetamine dependence, but also to the development of methamphetamine psychosis. A study on the human BDNF gene has demonstrated that the Val66Met BDNF gene polymorphism is associated with methamphetamine dependence in methamphetamine-dependent Taiwanese subjects ($p=0.046$), suggesting that homozygous carriers of the 196G allele are more susceptible to methamphetamine abuse (Cheng et al., 2005). This finding suggested that the Val66Met BDNF polymorphism may confer risk for substance abuse. In the present study, we examined the association of Val66Met BDNF with methamphetamine dependence and the occurrence of psychosis in a methamphetamine-dependent Malaysian male population. Besides that, the age of onset of methamphetamine dependence was also examined in the study.

2. Results

Results from RFLP indicated that three variants exist in the digestion product: homozygous 66Val (GG), heterozygous (GA), and homozygous 66Met (AA) (Fig. 1). The presence of 168-bp and 75-bp bands indicated the existence of the A (66Met) allele; the presence of a 243-bp band indicated the existence of the G (66Val) allele; and the presence of 75-bp, 168-bp, and 243-bp

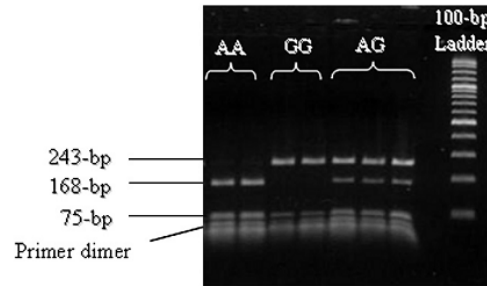


Fig. 1 – Gel photo of 2.5% (w/v) agarose gel electrophoresis for detection of BDNF Val66Met polymorphism.

bands indicated the existence of the AG (66Met/66Val) heterozygote. The 100-bp ladder was used as a DNA marker. The products of the RFLP were randomly selected to perform direct DNA sequencing for validation.

The frequencies of alleles and genotypes for controls and methamphetamine-dependent subjects are shown in Table 1. The genotype distribution in both controls and methamphetamine-dependent subjects fulfilled the Hardy–Weinberg equilibrium. For the Malaysian Chinese population, the differences in the genotype frequency ($p=0.016$) and allele frequency ($p=0.015$) between male controls and male methamphetamine-dependent subjects were found to be significant (Table 1). The frequency of carrying the G allele in methamphetamine-dependent subjects was significantly higher ($p=0.015$, odds ratio: 2.6, 95% CI 1.259–5.431) than in the controls. Comparison of the 66Val/66Val genotype with 66Val/66Met plus the 66Met/66Met genotype, revealed that the homozygous carriers of 66Val allele has 4.6 times more risk of being dependent on methamphetamine ($p=0.018$, odds ratio: 4.6, 95% CI 1.424–15.141). Furthermore, comparison between 66Val/66Val with 66Met/66Met showed a significantly increased odds ratio ($p=0.021$, odds ratio: 10.0, 95% CI 1.6–60.9) than in the controls. However, for the overall data and the data of other races, no significant difference was observed.

With regard to the occurrence of methamphetamine psychosis, no significant difference in either genotype frequency ($p=0.850$) or allele frequency ($p=0.889$) was seen when comparing methamphetamine-dependent subjects who experience psychosis with those who do not. However, examination of the data according to the ethnicities revealed that there was a significant difference in allele frequency in the Chinese methamphetamine-dependent subjects ($p=0.034$) (Table 2). The frequency of carrying the A allele in Chinese methamphetamine-dependent subjects with psychosis was higher than in the methamphetamine-dependent subjects without psychosis. Comparison of the 66Val allele frequency with 66Met allele frequency revealed a significant difference in odds ratio (OR: 0.2, 95% CI 0.07–0.86, $p=0.034$). The results showed no significant difference in genotype and allele frequency between methamphetamine-dependent subjects with and without psychosis among the other races studied.

Moreover, the effect of the BDNF Val66Met genetic polymorphism on the age of onset of methamphetamine abuse was also analyzed in 187 methamphetamine-dependent subjects. The mean age of onset for the methamphetamine-dependent groups was 24.8 ± 9.0 years old for BDNF 66Val/66Val ($n=57$), 23.2 ± 9.4 years old for BDNF 66Val/66Met ($n=99$), and 23.4 ± 5.9 years old for BDNF 66Met/66Met ($n=31$). For the age of onset among the Chinese dependent group, the mean age was 30.3 ± 8.5 years old for BDNF 66Val/66Val ($n=10$), 32.1 ± 11.493 years old for BDNF 66Val/66Met ($n=12$), and 24.0 ± 11.314 years old for BDNF 66Met/66Met ($n=2$). The age of onset of the methamphetamine-dependent subjects neither in overall dependent subjects ($p=0.539$) nor in Chinese ($p=0.593$), Malay ($p=0.822$), and Kadazan-Dusun ($p=0.762$) and Bajau ($p=0.371$) dependent subjects was not significant.

3. Discussion

Our findings failed to prove an association between BDNF Val66Met genotype or allele frequency and methamphetamine dependence in the overall Malaysian subjects studied. In a recent study in 189 methamphetamine abusers from a Japanese population (79.4% male and 20.6% female), BDNF Val66Met polymorphism was not associated with methamphetamine

Table 1 – Genotype and allelic frequencies of the BDNF Val66Met polymorphism in male controls and male methamphetamine-dependent subjects.

Ethnicity	Participant	Genotype			Allele frequency				OR (CI 95%)
		G/G	G/A	A/A	p	G	A	p	
Malay	Case subject	20 (0.339)	33 (0.559)	6 (0.102)	0.372	0.619	0.381	0.446	1.3 (0.75–2.20)
	Control	16 (0.314)	25 (0.490)	10 (0.196)		0.559	0.441		
Chinese	Case subject	10 (0.417)	12 (0.500)	2 (0.083)	0.016	0.667	0.333	0.015	2.6 (1.26–5.43)
	Control	6 (0.133)	27 (0.600)	12 (0.267)		0.433	0.567		
Kadazan-Dusun	Case subject	13 (0.260)	28 (0.560)	9 (0.180)	0.828	0.54	0.46	0.744	1.2 (0.62–2.23)
	Control	6 (0.200)	18 (0.600)	6 (0.200)		0.5	0.5		
Bajau	Case subject	13 (0.245)	26 (0.491)	14 (0.264)	0.859	0.491	0.509	0.703	0.8 (0.44–1.60)
	Control	8 (0.286)	14 (0.500)	6 (0.214)		0.536	0.464		
Total	Case subject	56 (0.301)	99 (0.532)	31 (0.167)	0.256	0.567	0.433	0.133	1.3 (0.94–1.73)
	Control	36 (0.234)	84 (0.545)	34 (0.221)		0.506	0.494		

Bold values represent significant p values.

Table 2 – Genotype and allelic frequencies of the BDNF Val66Met polymorphism in methamphetamine-dependent subjects with and without psychosis.

Ethnicity	Participant	Genotype			Allele frequency				OR (CI 95%)
		G/G	G/A	A/A	p	G	A	p	
Malay	Psychosis	10 (0.357)	15 (0.536)	3 (0.107)	0.942	0.625	0.375	0.956	1.1 (0.50–2.22)
	No psychosis	10 (0.323)	18 (0.581)	3 (0.097)		0.613	0.387		
Chinese	Psychosis	2 (0.182)	7 (0.636)	2 (0.182)	0.055	0.5	0.5	0.034*	0.2 (0.07–0.86)
	No psychosis	8 (0.615)	5 (0.385)	0 (0.000)		0.808	0.192		
Kadazan-Dusun	Psychosis	3 (0.214)	8 (0.572)	3 (0.214)	0.866	0.5	0.5	0.660*	0.8 (0.33–1.92)
	No psychosis	10 (0.278)	20 (0.555)	6 (0.167)		0.556	0.444		
Bajau Psychosis	Psychosis	4 (0.267)	8 (0.533)	3 (0.200)	0.801	0.533	0.467	0.736	1.3 (0.54–2.96)
	No psychosis	9 (0.237)	18 (0.474)	11 (0.289)		0.474	0.526		
Total	Psychosis	19 (0.279)	38 (0.559)	11 (0.162)	0.85	0.559	0.441	0.889	0.9 (0.62–1.45)
	No psychosis	37 (0.314)	61 (0.517)	20 (0.169)		0.572	0.428		

Bold values represent significant p values.

* The p value was calculated by using Fisher's exact test.

abuse (Itoh et al., 2005). In our study, although this association was not significant overall, the data for the Chinese subgroup suggested that the BDNF Val66Met polymorphism contributes to methamphetamine abuse vulnerability and methamphetamine dependence in this ethnicity. The risk for methamphetamine dependence in the Chinese subgroup with the 66Val169G allele was 2.6, whereas with the 66Val homozygous 196G, it was 4.6, suggesting that this allele may contribute to methamphetamine dependence in the male Chinese population.

Although the results of this study showed that the 66Val allele for the Chinese subpopulation is a risk factor for methamphetamine dependence, the age of onset for methamphetamine abuse from either the overall data or the Chinese dependent subjects within the three genotypes was not significant, inconsistent with the results of Cheng et al. (2005). They reported a significant difference in the age of onset for methamphetamine abuse across the three genotype groups ($p=0.048$), perhaps because of involvement of independent genes with a different penetrance level of different susceptibility loci in the pathogenesis of substance dependence.

In this study, the 66Met allele was less common in the Chinese methamphetamine-dependent groups than it was in the control group. However, the 66Val/66Val genotype is more common in methamphetamine-dependent groups, and this finding is also compatible with the observation from previous studies which was in Han Chinese population that the Met allele is the dominant allele of the BDNF Val66Met polymorphism (Cheng et al., 2005; Chen et al., 2004). Furthermore, the odds ratio of being methamphetamine dependent between 66Val/66Val and 66Val/66Met plus the 66Met/66Met genotype (OR=4.2) in this study also revealed that the Met allele is the dominant allele of the BDNF Val66Met polymorphism. This finding may indicate that the Chinese population in Malaysia and the Han Chinese have a common origin. The 66Val allelic frequency in our study for the Malaysian Chinese subgroup was 46.4%, comparable with previous findings that showed that the frequency of this allele in normal African-American, European-American, and Chinese people was 13.6%, 33.6%, and 46.7%, respectively. This result suggests that this allele is dominant in the Chinese and European-American population (Liu et al., 2005; Cheng et al., 2005).

Our overall data and stratified analyses by ethnicity showed that the BDNF Val66Met polymorphism was not associated with methamphetamine psychosis among the methamphetamine abusers, suggesting that this polymorphism does not cause susceptibility to psychosis in male Malaysian methamphetamine-dependent subjects. This finding is in line with the study of Itoh et al. (2005) that showed that the BDNF gene was not associated with methamphetamine psychosis in a Japanese population. Results of this study however, showed a significant difference in allele frequency between those who developed psychosis and those who do not in the Chinese methamphetamine-dependent subjects.

In contrast with the methamphetamine dependence, the risk for methamphetamine psychosis with the 66Val 196G allele was 0.2, while with 66Met 196A allele was 4.2 in Chinese methamphetamine-dependent subjects, whereas the methamphetamine dependence with the 66Val 196G allele was 2.6, suggesting that this 66Val allele is more likely to contribute to methamphetamine dependence in the male Chinese population but not for the methamphetamine psychosis. Moreover, 66Met allele may contribute to methamphetamine psychosis but not to methamphetamine dependence. This may be due to variation in definitions of psychosis that is being used in the present study compared to the ones that are being used in other studies, and it may, in part, be due to the small sample size of the methamphetamine psychosis in the present study.

Hall et al. (2003) in an animal study showed that heterozygous BDNF-knockout mice displayed cocaine-conditioned place preferences and reduced locomotion during habituation after cocaine injections. He reported that, compared with 66Met carriers, 66Val/66Val carriers may have higher levels of central BDNF, which increases the euphoric effect following methamphetamine administration and renders them more vulnerable to methamphetamine abuse. Our findings were similar to those of Hall et al. (2003) in that more case subjects than control subjects had the 66 Val variant.

There may be several explanations for the contrasting finding between the present study and that of Cheng et al. (2005). It is possible that our finding is a false positive which is contributed by the impact of stratification on our results.

However, this is not very likely because we do have a relatively homogenous group, especially in gender and the type of drug used, all our subjects being males (Table 3) who were on methamphetamine only.

In conclusion, our results failed to show any association between BDNF Val66Met polymorphism with occurrence of methamphetamine dependence, and with risk of psychosis in the total Malaysian population studied. However, a significant difference in the allelic and genotype frequencies was found in the Malaysian Chinese population for both methamphetamine dependence and psychosis. Our findings suggest that the 66Val/66Val genotype of the BDNF Val66Met polymorphism is a risk factor for methamphetamine dependence. Besides that, the BDNF 66Met allele may contribute to a vulnerability to methamphetamine psychosis in the Chinese population. Further study with a larger sample size may provide more evidence to confirm the genetic influence of BDNF in methamphetamine dependence.

4. Experimental procedures

4.1. Subject recruitment and sample collection

Samples from the case-control study were obtained from the psychiatric unit at the University Malaya Medical Centre (UMMC) and from a drug rehabilitation centre in Papar, Sabah that specializes in methamphetamine-dependent patients. The subjects included all patients who fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV; American Psychiatric Association, 1994) criteria for amphetamine and methamphetamine dependence. Methamphetamine dependence was confirmed by a positive urine test for methamphetamine during recruitment and the qualified psychiatrists from the two centres confirmed the presence or absence of psychosis. The subjects were considered to have psychosis if they have persecutory delusions and delusions of reference or present with auditory, visual hallucinations or tactile hallucinations. Subjects with mixed or unclear ethnicity and those with a history of psychiatric illness and other substance dependence were excluded.

The controls were obtained from healthy volunteers in the University of Malaya Medical Centre in Kuala Lumpur in West

Malaysia and from the Luyang Health Clinic, Sabah in East Malaysia. They were medically healthy with no history of chronic medical or surgical illness, had no previous history of psychiatric illness, and did not fulfil the DSM-IV criteria for amphetamine and methamphetamine dependence. The sample size was calculated using an online programme, namely Power of Association With Errors (PAWE) (Gordon et al., 2002; Gordon and Nothnagel, 2003). A total of 186 subjects ($n=186$) and 154 controls ($n=154$) comprising Malay, Chinese, Kadazan-Dusun, and Bajau ethnicities were recruited and consented to the study. Approval for the study was obtained from the UMMC Ethics Committee.

4.2. DNA preparation and analysis

Three millilitres of blood was collected from each participant by a standard method in an EDTA tube. DNA was extracted from leucocytes by using the QIAmp Blood Kit (Qiagen, Germany). In cases in which the participant was reluctant to provide blood samples, buccal swab tissues were obtained by the QIAmp Mini Kit (Qiagen, Germany). Genotyping of the Val66Met genetic polymorphism of the BDNF gene (G196A; rs6265) was performed by using polymerase chain reaction (PCR)-based methods with forward and reverse primers (forward, 5'-ACTCTGGAGAGCGTGAAT-3'; reverse, 5'-ATACTGTACACACAGGCTC-3', respectively). The PCR reaction was performed under the following conditions: 95 °C for 5 min; then 35 denaturing cycles of 30 s each at 95 °C, 30 s of annealing at the appropriate temperature, and 30 s each at 72 °C for extension, and final elongation at 72 °C for 10 min. PCR was carried out by using PCR Master Mix (Fermentas International Inc, Canada). Following that, the restriction fragment length polymorphism (RFLP) method was conducted with restriction enzyme NlaIII (New England Biolabs, USA). The PCR product was digested by NlaIII and the mixture was incubated at 37 °C in a dry-block heater overnight. The temperature was then increased to 65 °C for 20 min to terminate the activity of the enzyme. After the DNA was digested by restriction enzyme, products were loaded on 2.5% (w/v) agarose gel stained with GelRed (Biotium, USA) and then electrophoresed. The gel was viewed under UV light to observe restriction patterns. The size and distribution of the band was used to determine the genotype of the DNA sample. The PCR products were chosen randomly for validation by DNA sequencing.

Table 3 – Demographic and clinical characteristics of the subjects.

Characteristics	Malay (n=110)		Chinese (n=89)		Kadazan-Dusun (n=80)		Bajau (n=81)		Total (n=340)	
	Case (59)	Control (51)	Case (24)	Control (45)	Case (50)	Control (30)	Case (53)	Control (28)	Case (186)	Control (154)
Sex, N (%)										
Male	59 (100)	51 (100)	24 (100)	45 (100)	50 (100)	30 (100)	53 (100)	28 (100)	186 (100)	154 (100)
Age (years), mean (SD)	31 (7.8)	36 (10.6)	40 (9.6)	30 (94)	29 (6.6)	33 (13.1)	28 (6.4)	31 (16.7)	31 (8.2)	33 (12.2)
Onset age of meth dependence (years), mean(SD)	25 (9.1)		31 (10.1)		22 (7.6)		21 (7.1)		24 (8.8)	
Meth dependence										
With psytois, N (%)	28 (47.5)		11 (45.8)		14 (28)		15 (28.3)		68 (36.6)	
Without psychosis, N (%)	31 (52.5)		13 (54.2)		36 (72)		38 (71.7)		118 (63.4)	

4.3. Statistical analysis

Inter-group statistical analyses were performed by using the chi-square test and the Fisher's exact test, where necessary, to compare each ethnic group's cases with ethnically matched healthy controls for the frequencies of the BDNF 196G/G genotype, the 196G/A heterozygote, and the 196A/A genotype. The Fisher's exact test was performed when sample sizes were too small. For all analyses, *p* values of less than 0.05 were considered statistically significant.

Acknowledgments

This work was supported by Research University Grant FS151/2007C from the University of Malaya. The University of Malaya had no further role in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication. The authors thank the Kota Kinabalu Prison Centre and the Papar Rehabilitation Centre, Sabah, for their collaboration and permission to obtain samples from drug addicts; the Luyang Health Clinic, Kota Kinabalu, Sabah, for their permission to obtain samples from healthy controls; and Batoul Sadat Haerian, who assisted with the preparation and proof-reading of the manuscript. Dr. Rusdi Abdul Rashid and Dr. Amer Siddiq Amer Nordin from the Department of Psychological Medicine and Devika Chinayah and Yamunah Devi from the Department of Pharmacology, Faculty of Medicine, University of Malaya assisted with sample collection and interviews of the subjects of the study.

REFERENCES

- American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders fourth ed. American Psychiatric Press, Washington, DC.
- Chen, Z.Y., Patel, P.D., Sant, G., Meng, C.X., Teng, K.K., Hempstead, B.L., Lee, F.S., 2004. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J. Neurosci.* 24, 4401–4411.
- Cheng, C.Y., Hong, C.J., Yu, Y.W., Chen, T.J., Wu, H.C., Tsai, S.J., 2005. Brain-derived neurotrophic factor (Val66Met) genetic polymorphism is associated with substance abuse in males. *Brain Res. Mol. Brain Res.* 140, 86–90.
- Department of Statistics Malaysia, 2000. Percentage derived from the Population and Housing Census of Malaysia. Yearbook of Statistics, Sabah 2001.
- Diuzen, D.E., Story, G.M., Xu, K., Kucera, J., Walro, J.M., 1999. Alterations in nigrostriatal dopaminergic function within BDNF mutant mice. *Exp. Neurol.* 160, 500–507.
- Flanagin, B.A., Cook Jr., E.H., de Wit, H., 2006. An association study of the brain-derived neurotrophic factor Val66Met polymorphism and amphetamine response. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 141B, 576–583.
- Gordon, D., Nothnagel, M., 2003. Power for Association With Errors (PAWE) version 1.2. <http://linkage.rockefeller.edu/pawe/> 2003 Accessed on February 2003.
- Gordon, D., Finch, S.J., Nothnagel, M., Ott, J., 2002. Power and sample size calculations for case-control genetic association tests when errors present: application to single nucleotide polymorphisms. *Hum. Hered.* 54, 22–33.
- Haile, C.N., Kosten, T.R., Kosten, T.A., 2009. Pharmacogenetic treatments for drug addiction: cocaine, amphetamine and methamphetamine. *Am. J. Drug Alcohol Abuse* 35, 161–177.
- Hall, F.S., Drgonova, J., Goeb, M., Uhl, G.R., 2003. Reduced behavioral effects of cocaine in heterozygous brain-derived neurotrophic factor (BDNF) knockout mice. *Neuropsychopharmacology* 28, 1485–1490.
- Hofer, M., Pagliusi, S.R., Hohn, A., Leibrock, J., Barde, Y.A., 1990. Regional distribution of brain-derived neurotrophic factor mRNA in the adult mouse brain. *EMBO J.* 9, 2459–2464.
- Itoh, K., Hashimoto, K., Shimizu, E., Sekine, Y., Ozaki, N., Inada, T., Harano, M., Iwata, N., Komiya, T., Yamada, M., Sora, I., Nakata, K., Ujike, H., Iyo, M., 2005. Association study between brain-derived neurotrophic factor gene polymorphisms and methamphetamine abusers in Japan. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 132B, 70–73.
- Krebs, M.O., Guillin, O., Bourdell, M.C., Schwartz, J.C., Olie, J.P., Poirier, M.F., Sokoloff, P., 2000. Brain derived neurotrophic factor (BDNF) gene variants association with age at onset and therapeutic response in schizophrenia. *Mol. Psychiatry* 5, 558–562.
- Le Foll, B., Diaz, J., Sokoloff, P., 2005. A single cocaine exposure increases BDNF and D3 receptor expression: implications for drug-conditioning. *NeuroReport* 16, 175–178.
- Li, Y., Rowland, C., Tacey, K., Catanese, J., Sninsky, J., Hardy, J., Powell, J., Lovestone, S., Morris, J.C., Thal, L., Goate, A., Owen, M., Williams, J., Grupe, A., 2005. The BDNF Val66Met polymorphism is not associated with late onset Alzheimer's disease in three case-control samples. *Mol. Psychiatry* 10, 809–810.
- Liu, Q.R., Walther, D., Drgon, T., Polesskaya, O., Lesnick, T.G., Strain, K.J., de Andrade, M., Bower, J.H., Maraganore, D.M., Uhl, G.R., 2005. Human brain derived neurotrophic factor (BDNF) genes, splicing patterns, and assessments of associations with substance abuse and Parkinson's Disease. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 134B, 93–103.
- National Anti-Drug Agency, 2008. January–August 2008 Drug Report. Ministry of Home Affairs, Kuala Lumpur, Malaysia, pp. 1–37.
- Nestler, E.J., 2000. Genes and addiction. *Nat. Genet.* 26, 277–281.
- United Nations Information Service (UNIS), 2005. Launch of 2005 World Drug Report. <http://www.unis.unvienna.org/unis/en/pressconf/2005/pb20050629.html> 2005 Accessed on 29 June 2005.

MJP December 2008 Vol.17 No.2



Malaysian Journal of Psychiatry Ejournal

Dec 2008

Vol. 17 No. 2

CONTENTS

Editorial

Amphetamine Type Stimulant (ATS)
Induced Psychosis: A Rising Problems in
Malaysia.

3-6

Ahmad Hatim S

Original Paper

Validation of the Bahasa Malaysia
Version of the Coping Inventory for
Stressful Situation.

7-16

Ramli M
Mohd Ariff F
Khalid Y
Rosnani S

Social Anxiety Problem among Medical
Students in Universiti Malaya Medical
Center (UMMC) – A Cross-sectional
Study.

17-22

Salina M
Ng CG
Gill JS
Chin JM
Chin CJ
Yap WF

Student Learning Disability Experiences,
Training and Services Needs of
Secondary School Teachers.

23-36

Teoh HJ
Cheong SK
Woo PJ

Prevalence Of Obesity, Lipid and Glucose
Abnormalities in Outpatients Prescribed
Clozapine in University Malaya Medical
Center, Kuala Lumpur.

37-46

Sharmilla T
Ahmad Hatim S
Jambunathan ST

Impact of Psychiatry Training on Attitudes
of Undergraduate Medical Students.

47-54

Chandrasekaran R
Srikumar P. S
Joshua E
Rasamy G

Cross-Cultural Adaptation and Validation
of the Bahasa Malaysia Version of the
Eating Disorder Examination
Questionnaire (Ede-Q).

55-63

Ramli M
Jamaiyah H
Noor Azimah M
Khairani O
Adam B

The Prevalence of Depressive Symptoms
and Potential Risk Factors That May
Cause Depression among Adult Women
in Selangor.

64-72

Sherina MS
Rampal L
Azhar MZ

MJP December 2008 Vol.17 No.2

EDITORIAL

AMPHETAMINE TYPE STIMULANT (ATS) INDUCED PSYCHOSIS: A RISING PROBLEMS IN MALAYSIA

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The past decade has seen a marked increase in the popularity of ATS use, particularly methamphetamine, within East Asia, and the Pacific region (1) In Malaysia, the National Anti Drug Agency has identified 8,870 addicts (from January till August 2008) out of which 1,126 was ATS dependence. During the same period, the police have arrested 46,388 people under the Dangerous Drug Act 1952. They also has seize 283kg of syabu, 545kg of ecstasy powder, 66194 tablets of ecstasy pills and 222,376 tablets of yaba pills from Jan till August this year.(2)

The occurrence of psychosis arising from the use of ATS was first reported in the late 1930's. With growing ATS use, particularly methamphetamine, ATS-induced psychosis has become a major impact on public health.

Symptoms of ATS-induced psychosis

Methamphetamine use produces a variety of effects, ranging from irritability, to physical aggression, hyperawareness, hypervigilance, and psychomotor agitation. Repeated or high-dose use of the stimulant can cause drug-induced psychosis resembling paranoid schizophrenia, characterized by hallucinations, delusions and thought disorders.

When used in long term, methamphetamine may lead to development of psychiatric symptoms due to dopamine depletion in the striatum. The most common lifetime psychotic symptoms among methamphetamine psychotic patients – as reported in a cross-country study (3) involving Australia, Japan, the Philippines and Thailand – are persecutory delusion, auditory hallucinations, strange or unusual beliefs and thought reading. Those patients were also reported to suffer from impaired speech, psychomotor retardation, depression and anxiety.

An ATS psychosis can be distinguished from primary psychotic disorders by time. In ATS-induced psychosis symptoms usually resolve after the drug is discontinued. If symptoms do not resolve within 2 weeks after cessation of stimulant use, a primary psychiatric disorder should be suspected.(4)

When compared with other stimulants, such as cocaine, psychosis is induced more commonly by ATS, possibly due to the longer duration of action produced by amphetamines. For example, while smoking cocaine produces a “high” that lasts for 20-30 minutes, smoking methamphetamine produces a “high” that lasts 8-24 hours.(5)

MJP December 2008 Vol.17 No.2

Other symptoms of ATS-induced psychosis reported include affective blunting,(6) violent behavior, and self-mutilation and self-injurious behavior.(7)

Duration of ATS-induced psychotic state

Duration of amphetamine and methamphetamine-induced psychoses varies considerably. ATS-induced psychoses can be transient or persistent based on the duration of psychoses. In general, there are two types of methamphetamine psychosis.(8, 9)

- Transient type

The majority of ATS-induced psychosis is a shorter psychotic state that begins to improve along with changes in the acute central action of the stimulant. The psychotic symptoms of transient type ATS psychoses last only hours, and usually abate within a week of withdrawal from the drug. However, prolonged symptom episodes have been observed in some individuals.

- Persistent type

With this type of ATS psychoses, individuals experience psychotic symptoms for a considerably longer period of time. The psychotic state may last for more than 3 months and up to or beyond 6 months after cessation of drug use.

Prevalence of ATS-induced psychosis

ATS users are a high-risk population for psychosis.(10) Heavier methamphetamines users have been indicated to be at higher risk of psychosis compared with the general population.(9, 11) Methamphetamine users who already have a pre-existing proneness to psychosis are at particularly high risk of experiencing symptoms of psychosis.

Besides at risk of developing an ATS-induced psychosis, ATS users are also more prone to developing schizophrenia and other psychotic disorders.(10) Similarly, in people who are suffering from schizophrenia, methamphetamine use can precipitate and exacerbate psychotic symptoms.(12)

The high level of methamphetamine use has been associated with an increased prevalence in functional psychosis. This was demonstrated in two separate studies involving prison inmates who use stimulant drugs(11) and psychiatric patients (13) with a concurrent diagnosis of amphetamine abuse, respectively. Within these contexts, the prevalence of psychosis among individuals with amphetamine use disorder was up to 28%.

A more recent Australian study (14) further showed an alarmingly high prevalence of psychosis among methamphetamine users when compared with the general population, even among those who had no known history of schizophrenia or other psychotic disorders. Among participants screened, 13% were positive for psychosis compared with 1.2% in the general population (11 times greater in prevalence), and 23% had experienced a clinically significant symptom of suspiciousness, unusual thought content or hallucinations in the past year.

In addition, dependent methamphetamine users were noted to be three times more likely to have experienced psychotic symptoms than their non-dependent counterparts, even

MJP December 2008 Vol.17 No.2

after adjusting for history of schizophrenia and other psychotic disorders. (14) This clearly shows that dependent methamphetamine users are a particularly high-risk group for psychosis. Therefore, there is a strong need to have more local data and research on this important and rising public health problem.

References

1. Farrell M, Marsden J, Ali R, Ling W. Methamphetamine: drug use and psychoses becomes a major public health issue in the Asia Pacific region. *Addiction*. 2002 Jul;97(7):771-2.
2. Laporan Dadah Jan - Ogos 2008, Agensi Anti Dadah Kebangsaan. Available at <http://www.adk.gov.my/download/laporan/laporanog08.pdf>.
3. Srisurapanont M, Ali R, Marsden J, Sunga A, Wada K, Monteiro M. Psychotic symptoms in methamphetamine psychotic in-patients. *Int J Neuropsychopharmacol*. 2003 Dec; 6(4):347-52.
4. Larson M. Amphetamine related psychiatric disorders. *eMedicine*, Jan 29 2008. Available at: <http://www.emedicine.com/med/topic3114.htm>.
5. National Institute on Drug Abuse. Methamphetamine: abuse and addiction (NIH Publication No. 98 - 4210). Washington DC; April 1998.
6. Bell DS. Comparison Of Amphetamine Psychosis And Schizophrenia. *Br J Psychiatry*. 1965 Aug;111:701-7.
7. Kratochvil PH, Baberg HT, Dimsdale JE. Self-mutilation and severe self-injurious behavior associated with amphetamine psychosis. *Gen Hosp Psychiatry*. 1996 Mar;18(2):117-20.
8. Iwanami A, Sugiyama A, Kuroki N, Toda S, Kato N, Nakatani Y, et al. Patients with methamphetamine psychosis admitted to a psychiatric hospital in Japan. A preliminary report. *Acta Psychiatr Scand*. 1994 Jun;89(6):428-32.
9. Hall W, Hando J, Darke S, Ross J. Psychological morbidity and route of administration among amphetamine users in Sydney, Australia. *Addiction*. 1996 Jan;91(1):81-7.
10. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*. 1990 Nov 21;264(19):2511-8.
11. Farrell M, Boys A, Bebbington P, Brugha T, Coid J, Jenkins R, et al. Psychosis and drug dependence: results from a national survey of prisoners. *Br J Psychiatry*. 2002 Nov;181:393-8.

Appendix P - Publications

MJP December 2008 Vol.17 No.2

12. Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. *Br J Psychiatry*. 2004 Sep;185:196-204.
13. Dalmau A, Bergman B, Brismar B. Psychotic disorders among inpatients with abuse of cannabis, amphetamine and opiates. Do dopaminergic stimulants facilitate psychiatric illness? *Eur Psychiatry*. 1999 Nov;14(7):366-71.
14. McKetin R, McLaren J, Lubman DI, Hides L. The prevalence of psychotic symptoms among methamphetamine users. *Addiction*. 2006 Oct;101(10):1473-8.

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A Randomized, Placebo-Controlled Trial of Aripiprazole For The Treatment Of Methamphetamine Dependence and Associated Psychosis

Journal:	<i>International Journal of Psychiatry in Clinical Practice</i>
Manuscript ID:	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Sulaiman, Ahmad Hatim; University Malaya, Department of Psychological Medicine Gill, Jesjeet Singh; University Malaya, Department of Psychological Medicine Said, Mas Ayu; University Malaya, Department of Psychological Medicine Zainal, Nor Zuraida; University Malaya, Department of Psychological Medicine Habil, Mohamad Hussain; University Malaya, University Malaya Centre for Addiction Sciences Ng, Chong Guan; Faculty of Medicine, University Malaya, Department of Psychological Medicine; University Medical Centre, Julius Centre for Health Sciences and Primary Care
Keywords:	Randomized controlled trial , Methamphetamine dependence, Aripiprazole, Psychosis

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A Randomized, Placebo-Controlled Trial of Aripiprazole For The Treatment Of Methamphetamine Dependence and Associated Psychosis

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Running title: Aripiprazole for Methamphetamine Psychosis

ABSTRACT

Objectives: The objectives of this study were to determine the efficacy and safety of aripiprazole for treatment of psychosis, retention and abstinence in patients with methamphetamine dependence.

Methods: 37 methamphetamine dependent patients with history of psychosis was randomly assigned to aripiprazole (5-10mg daily, N=19) or placebo (N=18) for 8 weeks under double-blind conditions. Follow-up evaluation was scheduled on day 7, 14, 28, 42 day 56 after enrollment.

Results: Participants on aripiprazole were significantly retained longer in the treatment (48.7 days, SD=4.0) compared with placebo (37.1 days, SD=5.0). The Kaplan Meier survival analysis showed that participants in aripiprazole group were less likely to drop out of the study than the placebo group ($p = 0.02$, $\chi^2 = 5.3$). Psychotic symptoms were significantly decreased among those on aripiprazole as compared to placebo ($p < 0.05$). However, no statistically significance was found between aripiprazole and placebo in maintaining abstinence (generalised estimation equation (GEE) analysis, $p = 0.41$). There was no serious adverse event reported.

Conclusion: Aripiprazole was no more effective than placebo in maintaining abstinence from methamphetamine use. However, it facilitated treatment retention and reduced the severity of psychotic symptoms. Aripiprazole was generally safe and well tolerated.

Keywords: Randomized controlled trial, Methamphetamine dependence, Aripiprazole, Psychosis.

A Randomized, Placebo-Controlled Trial of Aripiprazole For The Treatment Of Methamphetamine Dependence and Associated Psychosis

INTRODUCTION

Methamphetamine is a psycho-stimulant that may lead to repeated use and dependence. Due to its wide availability and low cost, methamphetamine has become one of the most common consumed illicit substances not only locally in Malaysia but globally [1]. The widespread abuse of methamphetamine impacts society at various levels; from the individual, to the individual's family and to their community. Methamphetamine dependence gives rise to serious behavioural, medical and psychiatric consequences, imposing an immense burden on the medical, public health and criminal justice systems due to increased legal problems, violence, and high rates of HIV infection and hepatitis due to high risk sexual behaviour [2].

Though there is some evidence on psychotherapeutic interventions in the treatment of methamphetamine dependence, relapse rates still remain high [3]. While effective agonist and antagonist pharmacotherapies exist for opioid dependence, no pharmacological treatment has yet to be found to be effective and approved for the treatment of methamphetamine abuse or dependence [4].

A treatment that is able to normalize the altered systems due to methamphetamine abuse may have a beneficial clinical effect on methamphetamine dependence. A 'replacement' strategy for methamphetamine dependence, paralleling that for opioid dependence, would entail the use of partial agonists, which have significant receptor affinity but low intrinsic activity [5]. Under conditions of low neurotransmitter tone, as is observed for dopamine during initial abstinence from chronic stimulant administration [6,7] a partial agonist should produce some receptor stimulation, and may therefore function as a replacement medication. Conversely, this partial agonist would then act as an antagonist when there are higher levels of neurotransmitter present in the synapse, as would occur following use of a stimulant upon relapse.

Due to its unique mechanism of action, a partial agonist such as aripiprazole is hypothesized to be able to restore neurotransmitter balance and the normal function of the mesolimbic dopamine system [8], and thus a promising replacement medication for psychostimulant addiction and methamphetamine dependence. There are several pre-clinical animal and human studies on the effect of aripiprazole in psychostimulant abuse. In animals, it has been showed that aripiprazole inhibits motor hyperactivity induced by amphetamine and cocaine in mice, without causing significant motor impairment [9]. Withdrawal from repeated amphetamine administration has been shown to decrease the motivation to work for natural rewards in rats, a phenomenon thought to be associated with hypofunction of the mesolimbic dopamine system. Low doses of aripiprazole has been shown to prevent this effect, suggesting that aripiprazole may have a potential use as a treatment for the motivational effects during methamphetamine withdrawal [10].

In humans, aripiprazole has been studied in schizophrenic cocaine-dependent subjects. While traditional antipsychotic medications (i.e. D2 dopamine receptor antagonist) may leave patients with a shortage of dopamine activity, worsened by receptors that have already been damaged by chronic cocaine use [11], aripiprazole was able to reduce the actual cocaine use and lessen the desire for cocaine in this patient population [12]. In the context of amphetamine abuse and addiction, aripiprazole has been demonstrated to attenuate many of the abuse-related behavioral effects of d-amphetamine in healthy volunteers [13,14].

Due to the limited evidence available in the literature, this randomized, placebo controlled trial was carried out. It was a continuation of an open label 2 weeks study of aripiprazole for the

treatment of methamphetamine dependence and associated psychotic symptoms. Aripiprazole is an approved antipsychotic used for the treatment of schizophrenia and bipolar disorder in Malaysia. The primary hypotheses were that aripiprazole will produce higher maintenance of methamphetamine abstinence than placebo, as well as increase treatment retention. In addition to measures of efficacy, safety was assessed by monitoring of adverse events, movement-related side effects and psychotic symptoms.

METHODS

The study was conducted at the University Malaya Medical Centre, Kuala Lumpur, Malaysia. There were a total of 37 subjects from that had completed a previous 2 weeks open label trial with aripiprazole 10mg daily were included. All the subjects met the following inclusion criteria; aged 18 – 60 years; a DSM-IV diagnosis of methamphetamine dependence; history of methamphetamine use at least once a week for the prior 3 months; history of psychotic symptom prior to randomization; no other Axis I DSM-IV psychiatric diagnosis or dependence to other substances; willing and able to provide written informed consent; not currently taking any antipsychotics except for aripiprazole; currently not suicidal or homicidal; no serious medical illnesses; no known hypersensitivity or allergy to aripiprazole; and for females, not pregnant and willing to use an acceptable method of contraception for the duration of the study.

A battery of measures was used to determine the subjects' eligibility, treatment efficacy and safety. The MINI International Neuropsychiatric Interview - M.I.N.I. [15] was used to identify past and current psychiatric and substance use diagnoses based on DSM-IV criteria. It is used to assess suicidality. The Brief Substance Craving Scale - BSCA [16] was used to assess methamphetamine craving. Psychotic symptom severity was assessed using the Positive and Negative Symptoms Scale – PANSS [17] and the Clinical Global Impression Scale - CGI [18,19,20]. Extra-pyramidal symptoms were assessed by the Abnormal Involuntary Movement Scale – AIMS [21]; the Barnes Akathisia Scale – BAS [22], and the Simpson Angus Scale –SAS [23]. Demographic data and criminal history were also obtained.

Follow-up evaluation was scheduled on days 7, 14, 28, 42 day 56 after enrollment into the study. At each follow-up evaluation, urine toxicology was performed for methamphetamine, vital signs and weights were measured, and any adverse event was recorded. Assessment of the BSCA, PANSS and CGI scales were done on each visit. Assessment of the AIMS, BAS and SAS were done on baseline, day 14 and 42.

Eligible participants were randomly assigned to receive either aripiprazole or placebo for 8 weeks (56 days). In the active treatment arm, the patients were started on 10 mg aripiprazole at baseline, and were given flexible doses of 5-10 mg/day during the 8-week study. Dose reduction was permitted in the event of adverse effects. Upward titration following a dose reduction was also allowed.

The primary outcome of the study was the proportion of participants abstinent from methamphetamine use during each study visit based on urine toxicology results. Comparison between treatment groups were done using the logistic generalized estimating equations (GEE) regression model [24], with the assumptions that missing data are missing 'completely at random' [25]. Retention in treatment was measured as the number of days from the first dose of study medication at the time of randomization to the participant's last study visit during the 8-week medication treatment period. Differences in retention by treatment groups were evaluated using a Kaplan–Meier survival function.

Effect of treatment groups on continuous measures such as the PANSS, CGI, and BSCS were evaluated using a mixed model approach which produces unbiased results for the missing

values. For BSCS, a total methamphetamine craving score was calculated for each week by adding responses for intensity, frequency, and length of craving. Independent t-test was used to examine changes in mean scores of the AIMS, BAS and SAS from baseline. All participants were included in this intention-to-treat analysis. Univariate comparisons of baseline demographic and drug use between treatment group assignment were performed using independent t-test or Mann-Whitney test for continuous variables and Chi-square for categorical variables.

All the procedures in this study were in accordance with the ethical standards of the responsible local or national committee on human experimentation and with the Helsinki Declaration (1975, revised 1983).

RESULTS

A total of 49 patients participated in a 2-week open label study with aripiprazole. After 2 weeks of aripiprazole treatment, 37 patients fulfilled the inclusion criteria for this study and were recruited. A total of 19 patients were randomized to aripiprazole and 18 to placebo. The baseline characteristics of participants randomized to aripiprazole and placebo are shown on Table 1, while the drug history characteristics were shown on Table 2. There were no significant difference between the aripiprazole and placebo in terms of baseline demographic characteristics and previous drug history.

The maximum length of time in treatment was 56 days. There was a statistically significant difference between treatment groups in the number of days spent in treatment ($p < 0.05$), with those on aripiprazole retained for an average of 48.7 days (+ 4.0) compared with only 37.1 days (+ 5.0) for the placebo group. Time to dropout was also compared, where the survival curves showed that those on aripiprazole were significant less likely ($p < 0.05$) to drop out of the study (Figure 1).

More subjects on aripiprazole were methamphetamine-free as compared to placebo on all visits except on day 56 (Figure 2). However, logistic regression analysis with GEE shows that there was no significant difference between treatment groups at baseline, the rate of change over time, treatment and treatment over time (Table 3). Craving symptoms were measured by using the BSCS scales. There were statistically significant effects of the intervention using the BSCS scales in the MMRM (Table 4).

Psychopathology severity as measured by the PANSS decreased among participants on aripiprazole but increased in those on placebo, a difference that was statistically significant over time using the mixed model repeated measures (MMRM). The changes of PANSS over time were not significant. Similarly the CGI score decreased among participants on aripiprazole and increased on those on placebo, while increased in the placebo group. The subjects had an average CGI score of 2.0 and 2.1 in the aripiprazole and placebo groups, respectively at baseline. The scores reduced to normal in the aripiprazole arm while showing a worsening trend in the placebo group. In fact, four patients in the placebo arm (22.2%) developed worsening of psychotic symptoms during the study. There was again statistical significance between the treatment arm and treatment over time, but not purely on time alone (Table 4).

No serious AEs occurred during the study and no significant changes to vital signs were noted. Adverse events (AEs) reported in both groups were all mild to moderate in intensity, with no significant differences in the incidence of any AEs between aripiprazole and placebo. In the aripiprazole arm, akathisia, insomnia and agitation were the three most common AEs reported, while in the placebo arm, psychosis and insomnia were the two most common AEs reported (Table 5). There were no statistically significant changes between the aripiprazole and placebo arm in the occurrence of movement-related side effects as measured with BARS, AIMS and SAS scales. There were 7 patients from the aripiprazole arm and 3 from the placebo arm who received concomitant

medications. Lorazepam were given to 8 subjects; for agitation (1 from each arm), akathisia (4 from the aripiprazole arm) and insomnia (2 from the placebo arm). Zolpidem for insomnia was given to 1 subject on aripiprazole; and escitalopram was prescribed to 1 subject also on aripiprazole for depression.

DISCUSSION

This study demonstrated a significant benefit of aripiprazole in retention of patients in treatment although no significant effect was seen in abstinence. On the secondary outcome measures, treatment with aripiprazole showed significant reduction in methamphetamine craving and psychotic symptom severity as compared to placebo. There was no significant difference in the safety measurement between the two treatment arms.

These results indicate that although some patients in the aripiprazole arm continued to use methamphetamine, the majority of them returned for the scheduled evaluation visits, with only 3 patients lost to follow up. This has a potentially positive implication. One of the most significant problems for the long-term treatment of stimulant dependence is the high incidence of relapse to drug seeking and drug taking following abstinence [26, 27]. By being able to be retained longer in treatment, patients have a greater opportunity to receive frequent health services provided by their doctors and therefore can be given psychological or behavioural therapies to improve treatment outcome.

Two previous studies that compared aripiprazole and placebo showed that the antipsychotic failed to treat methamphetamine dependence [28,29]. Unlike these studies, our study managed to show that aripiprazole is at least significantly more effective than placebo in keeping patients in treatment and improving psychotic symptoms. The difference in our findings and theirs may possibly due to several differences in the study designs, in terms of the study population, route of administration of methamphetamine and dosage used. Our study included subjects who are methamphetamine dependent with psychotic symptoms, whereas the subjects from the earlier two studies were without psychosis. The subjects in our study are more likely to represent the type of patients physicians see in the real clinical settings. The study population in the previous studies used methamphetamine intravenously, while patients in our study used methamphetamine via smoking/nasal and oral routes. Different routes of methamphetamine administration may have different pharmacological effects that result in the urge for repeated use of the stimulant. Ethnic differences could also account for the disparity between this study and the other two. The earlier studies involved Caucasian subjects while ours were an Asian sample. The pharmacokinetics and pharmacodynamics of aripiprazole may vary across different ethnic populations. In terms of dosage, our study used a lower and flexible dose of 5-10 mg of aripiprazole once daily. The earlier studies used a fixed dose 15 mg. The more intense withdrawal symptoms caused by a higher dose of aripiprazole might have possibly 'forced' patients to increase methamphetamine use to overcome symptoms. Furthermore, patients in our study also underwent detoxification for 2 weeks with aripiprazole together with other symptomatic treatment (e.g. benzodiazepine) prior to randomisation to aripiprazole or placebo. The patients in our study were severely dependent with at least 3 months of history of drug use, thus making them practically similar to that found in real-life settings. Therefore this study can be considered more of an effectiveness study rather than an efficacy study alone.

The use of partial dopamine agonists may be an effective treatment for stimulant dependence [5]. Aripiprazole has been shown to reduce craving among schizophrenic with cocaine dependence [12], but in another study on methamphetamine addiction, it was found that aripiprazole 15 mg daily was no different from placebo [29]. It is possible that our study had a positive outcome as the dose used was lower, as smaller doses has been suggested by others [13,14,29]. As mentioned earlier, a partial dopamineagonist such as aripiprazole produces some

stimulation at the D2 receptors, and may therefore act as a replacement medication during the initial abstinence from chronic stimulant use. When there are higher levels of neurotransmitter present in the synapse, as would occur following the use of methamphetamine upon relapse, aripiprazole would then act as an antagonist. Therefore using aripiprazole to treat methamphetamine dependence may be able to block the acute stimulant abuse-related effects, thereby extinguishing drug-seeking and drug-taking behaviours over time. However, there is an inherent limitation in using competitive antagonist where drug-dependent patients may increase self-administration of the stimulant drug to offset the effects of the antagonist, leading to continued use of the stimulant [8]. This could be a possible explanation on why some of patients in this study continued to use methamphetamine while on aripiprazole treatment.

The dose of aripiprazole used in this study was relatively low 5-10 mg/day. An earlier study showed that 10 mg aripiprazole is a reasonable starting dose for the treatment of stimulant abuse and dependence. It was shown that, aripiprazole given at 10 mg was not effective at attenuating the discriminative-stimulus effects of d-amphetamine in healthy volunteers, but was able to reduce some positive subject-rated effects produced by d-amphetamine [14]. This may explain why aripiprazole, even at lower doses, was able to attenuate some of the behavioural effects of methamphetamine dependent patients in our study, resulting in better retention rates compared to placebo.

Aripiprazole is an antipsychotic proven to be successful in the pharmacological treatment of psychotic symptoms in schizophrenia [30]. This study demonstrated the significant effects of aripiprazole on psychotic symptoms among methamphetamine dependent patients. Both the PANSS and CGI scores decreased significantly in the aripiprazole-treated subjects. Positive symptoms in schizophrenia are hypothesised to result from excess subcortical dopamine release [30], whereas disturbed mesolimbic dopamine neurotransmission is believed to play a major role in psychostimulant dependence [31]. It is possible that aripiprazole counteracts the high dopamine levels found during the binge periods of the dependence cycle that causes psychotic symptoms, and thus exert its effect on those symptoms.

In our study, aripiprazole appeared to be safe and well tolerated for the treatment of methamphetamine dependence. No medication-related serious AE was reported in patients treated with aripiprazole. Nevertheless, there were incidences of mild-to-moderate and transient akathisia and agitation in both treatment arms, with the aripiprazole arm reporting a higher incidence than in the placebo group. In general, atypical antipsychotics are less likely to cause movement-related side effects, such as tardive dyskinesia, but may be associated with other adverse effects, including weight gain, sedation, increased levels of prolactin, and glucose and lipid dysregulation [32,33]. Earlier research that compared aripiprazole with other atypical antipsychotics found there was less weight gain, no hyperprolactinaemia and a lower risk for diabetes and hyperlipidaemia with aripiprazole [34,35,36].

Considering all outcomes in this study, aripiprazole was effective in retaining patients in treatment, reducing methamphetamine cravings, improving psychotic and anxiety symptoms, but was not effective in maintaining abstinence. However, we are yet able to draw any definite conclusions on its potential efficacy in relapse prevention among detoxified patients. Future research with larger number of subjects and with a longer duration is needed to ascertain the therapeutic effect of aripiprazole in methamphetamine dependence.

We do recognize some limitations of this study. Firstly, findings were limited by the small sample size. In part, it was due to the restrictive eligibility criteria and limited financial budget. Secondly, 8 weeks may be too short a duration to observe the true effectiveness of aripiprazole. Thirdly, the findings of this study could only be generalized with caution as the study population was from the outpatient clinic located in a hospital in Kuala Lumpur. The study population could differ

from the patients in the community because of the treatment seeking behavior. For a better generalization of the findings, it would be ideal to conduct a community survey. Lastly, no behavioural measures of reinforcement intervention were incorporated into design of this study. While medications are intended to reduce drug-taking behaviour, other studies have shown modification of subjective effects requires behavioural measures of reinforcement, e.g. drug self-administration or the multiple-choice procedures [37,38].

DISCLOSURE OF INTEREST

None to declare

REFERENCES

1. United Nations Office of Drugs on Crime (UNODC). 2007 World Drug Report. Vienna, Austria: UNODC; 2007.
2. Hando J, Hall W. HIV risk-taking behaviour among amphetamine users in Sydney, Australia. *Addiction* 1994; 89(1): 79-85.
3. Rawson RA, Gonzales R, Brethen P. Treatment of methamphetamine use disorders: an update. *J Subst Abuse Treat* 2002; 23(2): 145-50.
4. Grabowski J, Shearer J, Merrill J, Negus SS. Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. *Addict Behav* 2004; 29(7): 1439-64.
5. Childress AR, O'Brien CP. Dopamine receptor partial agonists could address the duality of cocaine craving. *Trends Pharmacol Sci* 2000; 21(1): 6-9.
6. Volkow ND, Chang L, Wang G J, Fowler JS, Leonido-Yee M, Franceschi D, Sedler MJ, Gatley SJ, Hitzemann R, Ding YS, Logan J, Wong C, Miller EN. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry* 2001; 158(3): 377-82.
7. Weiss F, Markou A, Lorang MT, Koob GF. Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. *Brain Res* 1992; 593(2): 314-8.
8. Lile JA, Stoops WW, Vansickel AR, Glaser PE, Hays LR, Rush CR. Aripiprazole attenuates the discriminative-stimulus and subject-rated effects of D-amphetamine in humans. *Neuropsychopharmacology* 2005; 30(11): 2103-14.
9. Leite JV, Guimaraes FS, Moreira FA. Aripiprazole, an atypical antipsychotic, prevents the motor hyperactivity induced by psychotomimetics and psychostimulants in mice. *Eur J Pharmacol* 2008; 578(2-3): 222-7.
10. Schwabe K, Koch M. Effects of aripiprazole on operant responding for a natural reward after psychostimulant withdrawal in rats. *Psychopharmacology (Berl)* 2007; 191(3): 759-65.
11. Zimmet SV, Strous RD, Burgess ES, Kohnstamm S, Green AI. Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. *J Clin Psychopharmacol* 2000; 20(1): 94-8.
12. Beresford TP, Clapp L, Martin B, Wiberg JL, Alfors J, Beresford HF. Aripiprazole in schizophrenia with cocaine dependence: a pilot study. *J Clin Psychopharmacol* 2005; 25(4): 363-6.
13. Stoops WW. Aripiprazole as a potential pharmacotherapy for stimulant dependence: human laboratory studies with d-amphetamine. *Exp Clin Psychopharmacol* 2006; 14(4): 413-21.
14. Stoops WW, Lile JA, Glaser PE, Rush CR. A low dose of aripiprazole attenuates the subject-rated effects of d-amphetamine. *Drug Alcohol Depend* 2006; 84(2): 206-9.
15. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59 (20): 22-33; quiz 34-57.

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16. Somoza EBS, Himmler C Et Al. The Brief Substance Craving Scale—measuring craving in clinical trials. NIDA Res Monogr. 1999; 180:304.
17. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; 13(2): 261-76.
18. Guy W. ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publ No ADM 76-338). Rockville, MD 1976; page 218-222 U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs.
19. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, Rodriguez MJ, Rele R, Orta J, Kharbeng A, Araya S, Gervin M, Alonso J, Mavreas V, Lavrentzou E, Lontos N, Gregor K, Jones PB. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta Psychiatr Scand Suppl* 2003; 416:16-23.
20. Huber CG, Lambert M, Naber D, Schacht A, Hundemer HP, Wagner TT, Schimmelmann BG. Validation of a Clinical Global Impression Scale for Aggression (CGI-A) in a sample of 558 psychiatric patients. *Schizophr Res* 2008; 100(1-3): 342-8.
21. Rush JA. Abnormal Involuntary Movement Scale (AIMS). in *Handbook of Psychiatric Measures* 2000: 166-168 American Psychiatric Association.
22. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989; 154:672-6.
23. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 1970; Suppl, 212:11-9.
24. McCullagh P. Regression models for ordinal data (with discussion). *J R Stat Soc Ser B* 1980;42: 109-142.
25. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*, 2nd edn. John Wiley & Sons Inc.: Hoboken, NJ. 2002.
26. Dackis CA, O'Brien CP. Cocaine dependence: a disease of the brain's reward centers. *J Subst Abuse Treat* 2001; 21(3): 111-7.
27. Wagner FA, Anthony JC. From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* 2002; 26(4): 479-88.
28. Tiihonen J, Kuoppasalmi K, Fohr J, Tuomola P, Kuikanmaki O, Vormo H, Sokero P, Haukka J, Meririnne E. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *Am J Psychiatry* 2007; 164(1): 160-2.
29. Newton TF, Reid MS, De La Garza R, Mahoney JJ, Abad A, Condos R, Palamar J, Halkitis PN, Mojisak J, Anderson A, Li SH, Elkashef A. Evaluation of subjective effects of aripiprazole and methamphetamine in methamphetamine-dependent volunteers. *Int J Neuropsychopharmacol* 2008; 11(8): 1037-45.
30. Taylor DM. Aripiprazole: a review of its pharmacology and clinical use. *Int J Clin Pract* 2003; 57(1): 49-54.
31. Pulvirenti L, Koob GF. Being partial to psychostimulant addiction therapy. *Trends Pharmacol Sci* 2002; 23(4): 151-3.
32. Srisurapanont M, Maneeton B, Maneeton N. Quetiapine for schizophrenia. *Cochrane Database Syst Rev* 2004;(2). CD000967.
33. Hunter RH, Joy CB, Kennedy E, Gilbody SM, Song F. Risperidone versus typical antipsychotic medication for schizophrenia. *Cochrane Database Syst Rev* 2003; (2). CD000440.
34. Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, Saha A, Ali M, Iwamoto T. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res* 2003; 61(2-3): 123-36.
35. McQuade RD, Stock E, Marcus R, Jody D, Gharbia NA, Vanveggel S, Archibald D, Carson WH. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry* 2004; 65 (18): 47-56.

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36. Chrzanowski WK, Marcus RN, Torbeyns A, Nyilas M, McQuade RD. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. *Psychopharmacology (Berl)* 2006; 189(2): 259-66.
37. Fischman MW, Schuster CR. Cocaine self-administration in humans. *Fed Proc* 1982; 41(2): 241-6.
38. Griffiths RR, Troisi JR, Silverman K, Mumford GK. Multiple-choice procedure: an efficient approach for investigating drug reinforcement in humans. *Behav Pharmacol* 1993; 4(1): 3-13.

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Table 1 Baseline sociodemographic characteristics of methamphetamine dependence subjects

Variables	Aripiprazole (n=19)	Placebo (n=18)	p value
Age, mean \pm SD	35.5 \pm 8.5	32.9 \pm 8.4	p >0.05
Gender, %			
Male	94.7 (18)	94.4 (17)	p >0.05
Female	5.3 (1)	5.6 (1)	
Ethnic, %			
Malay	57.9 (11)	72.2 (13)	p >0.05
Chinese	31.6 (6)	16.7 (3)	
Indian	10.5 (2)	11.1 (2)	
Marital Status, %			
Married	42.1 (8)	44.4 (8)	p >0.05
Single	42.1 (8)	38.9 (7)	
Divorced	15.8 (3)	16.7 (3)	
Education, %			
Tertiary	11.2 (2)	16.7 (3)	p >0.05
Secondary	77.8 (14)	77.7 (14)	
Primary	11.1 (2)	5.6 (1)	
Employment, %			
Full time	78.9 (15)	83.3 (15)	p >0.05
Part time	0	5.6 (1)	
Student	0	5.6 (1)	
Unemployed	21.4 (4)	5.6 (1)	
Income, mean \pm SD (in Ringgit Malaysia per month)	8,047 \pm 23,172	3,441 \pm 4,801	p >0.05¶
Number of sibling, mean \pm SD	4.9 \pm 2.8	5.5 \pm 2.5	p >0.05

¶Reference group

¶Mann-Whitney U Test

Table 2 Drug use characteristics of the study subjects

Variables	Aripiprazole (n=19)	Placebo (n=18)	p value
Years methamphetamine used, mean \pm SD	5.5 \pm 4.8	4.8 \pm 3.6	p>0.05
Age of first methamphetamine used, mean \pm SD	30.8 \pm 8.2	28.2 \pm 9.2	p>0.05
Amount of money spend monthly for methamphetamine, mean \pm SD in Ringgit Malaysia	1,311 \pm 1,320	1,611 \pm 2,295	p>0.05¶
Route of methamphetamine, (%)			
Smoking	61.1 (11)	55.6 (10)	p>0.05
Nasal	27.8 (5)	38.9 (7)	
#Oral	8.3 (3)	5.6 (1)	
Nicotine dependence,(%)	83.3 (15)	88.9 (16)	p>0.05
Alcohol abuse,(%)	5.3 (1)	5.6 (1)	p>0.05
Cannabis abuse,(%)	27.8 (5)	50.0 (9)	p>0.05

#Reference group

¶Mann-Whitney U Test

Table 3 Generalized Estimating Equations (GEE) analysis for methamphetamine urine screens between aripiprazole and placebo

Source	Type III		
	Wald Chi-Square	df	Sig.
Intercept (Baseline)	0.36	1	0.549
Visit (Rate of change over time)	3.75	4	0.441
Group (Treatment)	1.86	1	0.173
Visit * Group (treatment over time)	3.94	4	0.415
Dependent Variable: Urine Model: (Intercept), Visit (Baseline, day 7,14, 28, 42 and 56), Group (aripiprazole and placebo), Visit * Group			

Table 4 Mixed Model Repeated Measures (MMRM) for PANSS, CGI, and BSCS by the treatment condition

Source	PANSS		CGI		BSCS	
	F	Sig.	F	Sig.	F	Sig.
Intercept	413.74	0.001	44.54	0.001	42.11	0.001
Intervention * Time	6.26	0.004	3.48	0.037	1.62	0.159
Intervention	4.94	0.032	6.68	0.014	6.51	0.015
Time	0.19	0.825	2.87	0.065	1.73	0.133

Dependent Variable: PANSS and CGI

Model for PANSS and CGI: (Intercept), Time (Baseline, day 14 and 56), Intervention (aripiprazole and placebo), Intervention * Time

Model for BSCS: (Intercept), Time (Baseline, day 7, 14, 28, 42 and 56), Intervention (aripiprazole and placebo), Intervention * Time

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Table 5 Frequency of adverse events reported by treatment condition

Adverse Events	Aripiprazole (n=19)	Placebo (n=18)	Total (37)
Akathasia	26.6 (5)	5.6(1)	16.2 (6)
Insomnia	10.6 (2)	11.1 (2)	4 (10.8)
Agitation	10.6 (2)	5.6 (1)	3 (8.1)
Urinary Retention	5.3 (1)	0	1 (2.7)
Depression	5.3 (1)	0	1 (2.7)
Psychosis	0	22.2 (4)	4 (10.8)
Lethargy	0	5.6 (1)	1 (2.7)
Sedation	0	5.6 (1)	1 (2.7)
Sexual Dysfunction	0	5.6 (1)	1 (2.7)

p > 0.05 (Fisher's Exact test) on all items

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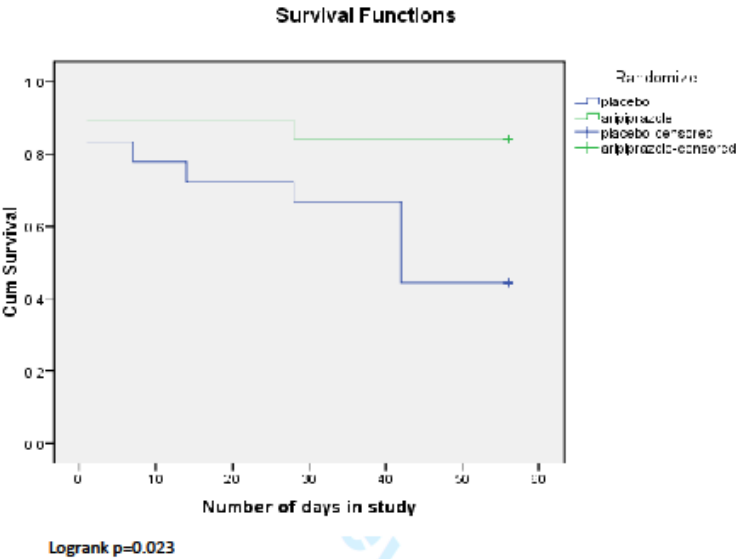
Key points:

1. Aripiprazole was no more effective than placebo in maintaining abstinence from methamphetamine use.
2. Aripiprazole facilitated treatment retention among subjects with methamphetamine dependence
3. Aripiprazole reduced the severity of psychotic symptoms among subjects with methamphetamine dependence with psychosis.
4. Aripiprazole was generally safe and well tolerated among methamphetamine dependence subjects.

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Figure 1 Kaplan-Meier estimate of the survivor function for retention in treatment



Means and Medians for Survival Time						
Randomize	Mean	95% C.I.		Median	95% C.I.	
Placebo	37.11	(27.14,	47.09)	42.0	(27.54,	56.46)
Aripiprazole	48.74	(40.86,	56.62)			
Overall	43.08	(36.50,	49.67)			

Figure 2 Methamphetamine positive urine screens by visit

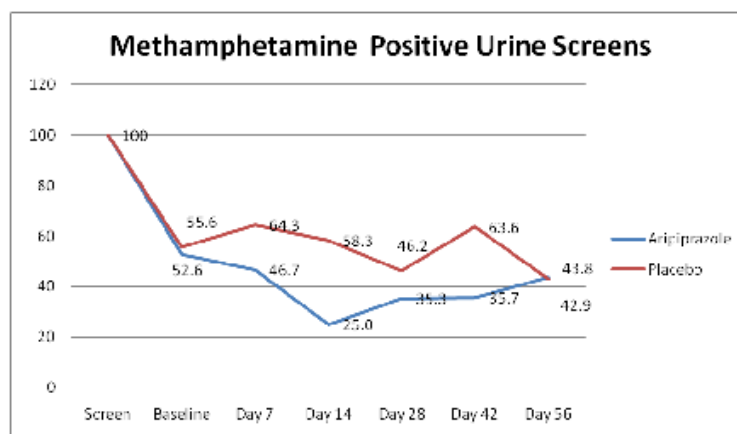


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Sedation	0	5.6 (1)	1 (2.7)
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p > 0.05 (Fisher's Exact test) on all items

References

- Adk (2009) Laporan Dadah Disember 2009: Bahagian Dasar, Perancangan dan Penyelidikan. Agensi Antidadah Kebangsaan Malaysia.
- Adson, D. E., Kushner, M. G. & Fahnhorst, T. A. (2005) Treatment of residual anxiety symptoms with adjunctive aripiprazole in depressed patients taking selective serotonin reuptake inhibitors. *J Affect Disord*, **86**(1). 99-104.
- Afp. (2000) Malaysia-drugs: Malaysia declares war on drugs, appeals for public support [cited 15 January 2011]; Available from: <http://www.aegis.com/NEWS/AFP/2000/AF000676.html>.
- Aharonovich, E., Nunes, E. & Hasin, D. (2003) Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug Alcohol Depend*, **71**(2). 207-11.
- Akta. (1952) Law of Malaysia. Dangerous Drug Act [cited 12 October, 2010]; Available from: <http://www.agc.gov.my/Akta/Vol.%205/Act%20234.pdf>.
- Albertson, T. E., Derlet, R. W. & Van Hoozen, B. E. (1999) Methamphetamine and the expanding complications of amphetamines. *West J Med*, **170**(4). 214-9.
- Albertson, T. E., Walby, W. F. & Derlet, R. W. (1995) Stimulant-induced pulmonary toxicity. *Chest*, **108**(4). 1140-9.
- Angrist, B., Sathananthan, G., Wilk, S. & Gershon, S. (1974) Amphetamine psychosis: behavioral and biochemical aspects. *J Psychiatr Res*, **11**:13-23.
- Anonymous (2004) Methamphetamine abuse. *Med Lett Drugs Ther*, **46**(1188). 62-3.
- Apa (1994) *Diagnostic and Statistical Manual of Mental Disorders. 4th ed*, American Psychiatric Association. American Psychiatric Press, Washington, DC.
- Arnett, E. N., Battle, W. E., Russo, J. V. & Roberts, W. C. (1976) Intravenous injection of talc-containing drugs intended for oral use. A cause of pulmonary granulomatosis and pulmonary hypertension. *Am J Med*, **60**(5). 711-8.
- Baker, A., Lee, N. K., Claire, M., Lewin, T. J., Grant, T., Pohlman, S., Saunders, J. B., Kay-Lambkin, F., Constable, P., Jenner, L. & Carr, V. J. (2005) Brief cognitive behavioural interventions for regular amphetamine users: a step in the right direction. *Addiction*, **100**(3). 367-78.

Bibliography

- Barnes, T. R. (1989) A rating scale for drug-induced akathisia. *Br J Psychiatry*, **154**:672-6.
- Baskin-Sommers, A. & Sommers, I. (2006) Methamphetamine use and violence among young adults *Journal of Criminal Justice*, **34**(6). 661-674.
- Baud, P., Arbilla, S., Cantrill, R. C., Scatton, B. & Langer, S. Z. (1985) Trace amines inhibit the electrically evoked release of [3H]acetylcholine from slices of rat striatum in the presence of pargyline: similarities between beta-phenylethylamine and amphetamine. *J Pharmacol Exp Ther*, **235**(1). 220-9.
- Bejerot, S., Ryden, E. M. & Arlinde, C. M. (2010) Two-year outcome of treatment with central stimulant medication in adult attention-deficit/hyperactivity disorder: a prospective study. *J Clin Psychiatry*, **71**(12). 1590-7.
- Beresford, T. P., Clapp, L., Martin, B., Wiberg, J. L., Alfors, J. & Beresford, H. F. (2005) Aripiprazole in schizophrenia with cocaine dependence: a pilot study. *J Clin Psychopharmacol*, **25**(4). 363-6.
- Bhattacharjee, J. & El-Sayeh, H. G. (2008) Aripiprazole versus typical antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev*, (3). CD006617.
- Bjelland, I., Dahl, A. A., Haug, T. T. & Neckelmann, D. (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*, **52**(2). 69-77.
- Bjorkenstam, C., Weitoft, G. R., Hjern, A., Nordstrom, P., Hallqvist, J. & Ljung, R. (2010) School grades, parental education and suicide--a national register-based cohort study. *J Epidemiol Community Health*, **95**(8). 402-412.
- Blockmans, D., Persoons, P., Van Houdenhove, B. & Bobbaers, H. (2006) Does methylphenidate reduce the symptoms of chronic fatigue syndrome? *Am J Med*, **119**(2). 167 e23-30.
- Borowsky, B., Adham, N., Jones, K. A., Raddatz, R., Artymyshyn, R., Ogozalek, K. L., Durkin, M. M., Lakhani, P. P., Bonini, J. A., Pathirana, S., Boyle, N., Pu, X., Kouranova, E., Lichtblau, H., Ochoa, F. Y., Branchek, T. A. & Gerald, C. (2001) Trace amines: identification of a family of mammalian G protein-coupled receptors. *Proc Natl Acad Sci U S A*, **98**(16). 8966-71.
- Brewer, D. D., Catalano, R. F., Haggerty, K., Gainey, R. R. & Fleming, C. B. (1998) A meta-analysis of predictors of continued drug use during and after treatment for opiate addiction. *Addiction*, **93**(1). 73-92.

Bibliography

Brooner, R. K., King, V. L., Kidorf, M., Schmidt, C. W., Jr. & Bigelow, G. E. (1997) Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Arch Gen Psychiatry*, **54**(1). 71-80.

Bruce, M. (2000) Managing amphetamine dependence. *Adv Psychiatr Treat*, **6**(1). 33-39.

Bruck, D., Kennedy, G. A., Cooper, A. & Apel, S. (2005) Diurnal actigraphy and stimulant efficacy in narcolepsy. *Human Psychopharmacology Clin Exp*, **20**:105-113.

Bureau.(2007) US Department of State,Bureau of International Narcotics and Law Enforcement Affairs: International Narcotics Control Strategy Report 2007 [cited 28 December 2010]; Available from:
<http://www.state.gov/p/inl/rls/nrcrpt/2007/vol1/html/80859.htm>.

Burris, K. D., Molski, T. F., Xu, C., Ryan, E., Tottori, K., Kikuchi, T., Yocca, F. D. & Molinoff, P. B. (2002) Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther*, **302**(1). 381-9.

Burti, L., Parolin, A. & Zanotelli, R. (1981) [Tardive dyskinesia. AIMS (Abnormal Involuntary Movement Scale) as a diagnostic and research tool]. *Minerva Med*, **72**(42). 2829-36.

Cadier, M. A. & Clarke, J. A. (1993) Ecstasy and Whizz at a rave resulting in a major burn plus complications. *Burns*, **19**(3). 239-40.

Cadoret, R. J., Troughton, E., O'gorman, T. W. & Heywood, E. (1986) An adoption study of genetic and environmental factors in drug abuse. *Arch Gen Psychiatry*, **43**(12). 1131-6.

Cadoret, R. J., Yates, W. R., Troughton, E., Woodworth, G. & Stewart, M. A. (1996) An adoption study of drug abuse/dependency in females. *Compr Psychiatry*, **37**(2). 88-94.

Callor, W. B., Petersen, E., Gray, D., Grey, T., Lamoreaux, T. & Bennett, P. J. (2005) Preliminary findings of noncompliance with psychotropic medication and prevalence of methamphetamine intoxication associated with suicide completion. *Crisis*, **26**(2). 78-84.

Carli, M., Tatarczynska, E., Cervo, L. & Samanin, R. (1993) Stimulation of hippocampal 5-HT_{1A} receptors causes amnesia and anxiolytic-like but not antidepressant-like effects in the rat. *Eur J Pharmacol*, **234**(2-3). 215-21.

Catanzarite, V. A. & Stein, D. A. (1995) 'Crystal' and pregnancy--methamphetamine-associated maternal deaths. *West J Med*, **162**(5). 454-7.

Bibliography

- Caton, C. L., Drake, R. E., Hasin, D. S., Dominguez, B., Shrout, P. E., Samet, S. & Schanzer, B. (2005) Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Arch Gen Psychiatry*, **62**(2). 137-45.
- Cernerud, L., Eriksson, M., Jonsson, B., Steneroth, G. & Zetterstrom, R. (1996) Amphetamine addiction during pregnancy: 14-year follow-up of growth and school performance. *Acta Paediatr*, **85**(2). 204-8.
- Chen, C. K., Hu, X., Lin, S. K., Sham, P. C., Loh El, W., Li, T., Murray, R. M. & Ball, D. M. (2004a) Association analysis of dopamine D2-like receptor genes and methamphetamine abuse. *Psychiatr Genet*, **14**(4). 223-6.
- Chen, C. K., Lin, S. K., Sham, P. C., Ball, D., Loh El, W. & Murray, R. M. (2005) Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *Am J Med Genet B Neuropsychiatr Genet*, **136**(1). 87-91.
- Chen, C. K., Lin, S. K., Sham, P. C., Ball, D., Loh, E. W., Hsiao, C. C., Chiang, Y. L., Ree, S. C., Lee, C. H. & Murray, R. M. (2003) Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychol Med*, **33**(8). 1407-14.
- Chen, Z. Y., Patel, P. D., Sant, G., Meng, C. X., Teng, K. K., Hempstead, B. L. & Lee, F. S. (2004b) Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci*, **24**(18). 4401-11.
- Cheng, C. Y., Hong, C. J., Yu, Y. W., Chen, T. J., Wu, H. C. & Tsai, S. J. (2005) Brain-derived neurotrophic factor (Val66Met) genetic polymorphism is associated with substance abuse in males. *Brain Res Mol Brain Res*, **140**(1-2). 86-90.
- Childress, A. R. & O'brien, C. P. (2000) Dopamine receptor partial agonists could address the duality of cocaine craving. *Trends Pharmacol Sci*, **21**(1). 6-9.
- Chou, P., Liou, M. Y., Lai, M. Y., Hsiao, M. L. & Chang, H. J. (1999) Time trend of substance use among adolescent students in Taiwan, 1991-1996. *J Formos Med Assoc*, **98**(12). 827-31.
- Christie, K. A., Burke, J. D., Jr., Regier, D. A., Rae, D. S., Boyd, J. H. & Locke, B. Z. (1988) Epidemiologic evidence for early onset of mental disorders and higher risk of drug abuse in young adults. *Am J Psychiatry*, **145**(8). 971-5.

Bibliography

Chrzanowski, W. K., Marcus, R. N., Torbeyns, A., Nyilas, M. & Mcquade, R. D. (2006) Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. *Psychopharmacology (Berl)*, **189**(2). 259-66.

Cogger S, M. R., Ross J, Et Al. (2008) *Methamphetamine Treatment Evaluation Study (MATES): Findings from the Brisbane Site, Technical Report No.295*, NDARC, New South Wales, Sydney.

Colfax, G., Vittinghoff, E., Husnik, M. J., Mckirnan, D., Buchbinder, S., Koblin, B., Celum, C., Chesney, M., Huang, Y., Mayer, K., Bozeman, S., Judson, F. N., Bryant, K. J. & Coates, T. J. (2004) Substance use and sexual risk: a participant- and episode-level analysis among a cohort of men who have sex with men. *Am J Epidemiol*, **159**(10). 1002-12.

Collinson, N. & Dawson, G. R. (1997) On the elevated plus-maze the anxiolytic-like effects of the 5-HT(1A) agonist, 8-OH-DPAT, but not the anxiogenic-like effects of the 5-HT(1A) partial agonist, buspirone, are blocked by the 5-HT1A antagonist, WAY 100635. *Psychopharmacology (Berl)*, **132**(1). 35-43.

Cooper, H. L., Brady, J. E., Ciccarone, D., Tempalski, B., Gostnell, K. & Friedman, S. R. (2007) Nationwide increase in the number of hospitalizations for illicit injection drug use-related infective endocarditis. *Clin Infect Dis*, **45**(9). 1200-3.

Correll, C. U. & Schenk, E. M. (2008) Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry*, **21**(2). 151-6.

Cretzmeyer, M., Sarrazin, M. V., Huber, D. L., Block, R. I. & Hall, J. A. (2003) Treatment of methamphetamine abuse: research findings and clinical directions. *J Subst Abuse Treat*, **24**(3). 267-77.

Cruickshank, C. C., Montebello, M. E., Dyer, K. R., Quigley, A., Blaszczyk, J., Tomkins, S. & Shand, D. (2008) A placebo-controlled trial of mirtazapine for the management of methamphetamine withdrawal. *Drug Alcohol Rev*, **27**(3). 326-33.

Curran, C., Byrappa, N. & McBride, A. (2004) Stimulant psychosis: systematic review. *Br J Psychiatry*, **185**:196-204.

Dackis, C. A. & O'brien, C. P. (2001) Cocaine dependence: a disease of the brain's reward centers. *J Subst Abuse Treat*, **21**(3). 111-7.

Dalmau, A., Bergman, B. & Brismar, B. (1999) Psychotic disorders among inpatients with abuse of cannabis, amphetamine and opiates. Do dopaminergic stimulants facilitate psychiatric illness? *Eur Psychiatry*, **14**(7). 366-71.

Bibliography

- De Silva, D. A., Wong, M. C., Lee, M. P., Chen, C. L. & Chang, H. M. (2007) Amphetamine-associated ischemic stroke: clinical presentation and proposed pathogenesis. *J Stroke Cerebrovasc Dis*, **16**(4). 185-6.
- Derlet, R. W. & Heischouer, B. (1990) Methamphetamine. Stimulant of the 1990s? *West J Med*, **153**(6). 625-8.
- Derlet, R. W., Rice, P., Horowitz, B. Z. & Lord, R. V. (1989) Amphetamine toxicity: experience with 127 cases. *J Emerg Med*, **7**(2). 157-61.
- Deykin, E. Y., Hsieh, C. C., Joshi, N. & Mcnamarra, J. J. (1986) Adolescent suicidal and self-destructive behavior. Results of an intervention study. *J Adolesc Health Care*, **7**(2). 88-95.
- Dhhs.(2001) National Household Survey on Drug Abuse. Chapter 5: Trends in Initiation of Substance Use. US Department of Health and Human Services [cited 21 November 2010]; Available from: <http://www.oas.samhsa.gov/nhsda/2k1nhsda/vol1/Chapter5.htm>.
- Dluzen, D. E., Story, G. M., Xu, K., Kucera, J. & Walro, J. M. (1999) Alterations in nigrostriatal dopaminergic function within BDNF mutant mice. *Exp Neurol*, **160**(2). 500-7.
- Doj (2010) *U.S. Department of Justice, National Drug Intelligence Center: National Drug Threat Assessment*. Washington DC.
- Dore, G. & Sweeting, M. (2006) Drug-induced psychosis associated with crystalline methamphetamine. *Australas Psychiatry*, **14**(1). 86-9.
- Drake, R. E., Mueser, K. T., Clark, R. E. & Wallach, M. A. (1996) The course, treatment, and outcome of substance disorder in persons with severe mental illness. *Am J Orthopsychiatry*, **66**(1). 42-51.
- Droogmans, S., Cosyns, B., D'haenen, H., Creten, E., Weytjens, C., Franken, P. R., Scott, B., Schoors, D., Kemdem, A., Close, L., Vandenbossche, J. L., Bechet, S. & Van Camp, G. (2007) Possible association between 3,4-methylenedioxymethamphetamine abuse and valvular heart disease. *Am J Cardiol*, **100**(9). 1442-5.
- Elkashef, A. M., Rawson, R. A., Anderson, A. L., Li, S. H., Holmes, T., Smith, E. V., Chiang, N., Kahn, R., Vocci, F., Ling, W., Pearce, V. J., Mccann, M., Campbell, J., Gorodetzky, C., Haning, W., Carlton, B., Mawhinney, J. & Weis, D. (2008) Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology*, **33**(5). 1162-70.
- Estroff, T. W., Dackis, C. A., Gold, M. S. & Pottash, A. L. (1985) Drug abuse and bipolar disorders. *Int J Psychiatry Med*, **15**(1). 37-40.

Bibliography

- Feinstein, A. R. (1970) The pre-therapeutic classification of co-morbidity in chronic disease. *Journal of Chronic Disease* **23**:455-468.
- Findling, R. L., Robb, A., Nyilas, M., Forbes, R. A., Jin, N., Ivanova, S., Marcus, R., Mcquade, R. D., Iwamoto, T. & Carson, W. H. (2008) A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *Am J Psychiatry*, **165**(11). 1432-41.
- Fischman, M. W. & Schuster, C. R. (1982) Cocaine self-administration in humans. *Fed Proc*, **41**(2). 241-6.
- Flanagan, J. M., Gerber, A. L., Cadet, J. L., Beutler, E. & Sipe, J. C. (2006) The fatty acid amide hydrolase 385 A/A (P129T) variant: haplotype analysis of an ancient missense mutation and validation of risk for drug addiction. *Hum Genet*, **120**(4). 581-8.
- Flanagin, B. A., Cook, E. H., Jr. & De Wit, H. (2006) An association study of the brain-derived neurotrophic factor Val66Met polymorphism and amphetamine response. *Am J Med Genet B Neuropsychiatr Genet*, **141**(6). 576-83.
- Gard, C. (2004) Methamphetamine: speeding toward psychosis: why meth may possibly be the worst of them all. . *Current Health* 2, **30**:25-27.
- George R.U., Gregory I.E., Michele C. L. & W.P., R.(2000) Genetic influences in drug abuse: Human Substance Abuse Vulnerability And Genetic Influences [cited 15 June 2010]; Available from: <http://www.acnp.org/g4/GN401000174/CH170.html>.
- Glasner-Edwards, S., Mooney, L. J., Marinelli-Casey, P., Hillhouse, M., Ang, A. & Rawson, R. (2008a) Clinical course and outcomes of methamphetamine-dependent adults with psychosis. *J Subst Abuse Treat*, **35**(4). 445-50.
- Glasner-Edwards, S., Mooney, L. J., Marinelli-Casey, P., Hillhouse, M., Ang, A. & Rawson, R. (2008b) Risk factors for suicide attempts in methamphetamine-dependent patients. *Am J Addict*, **17**(1). 24-7.
- Gonzales, R., Marinelli-Casey, P., Shoptaw, S., Ang, A. & Rawson, R. A. (2006) Hepatitis C virus infection among methamphetamine-dependent individuals in outpatient treatment. *J Subst Abuse Treat*, **31**(2). 195-202.
- Gordon, D., Finch, S. J., Nothnagel, M. & Ott, J. (2002) Power and sample size calculations for case-control genetic association tests when errors are present: application to single nucleotide polymorphisms. *Hum Hered*, **54**(1). 22-33.

Bibliography

Gordon, D., Levenstien, M. A., Finch, S. J. & Ott, J. (2003) Errors and linkage disequilibrium interact multiplicatively when computing sample sizes for genetic case-control association studies. *Pac Symp Biocomput*, **8**:490-501.

Grabowski, J., Shearer, J., Merrill, J. & Negus, S. S. (2004) Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. *Addict Behav*, **29**(7). 1439-64.

Gradus, J. L., Qin, P., Lincoln, A. K., Miller, M., Lawler, E., Sorensen, H. T. & Lash, T. L. (2010) Acute stress reaction and completed suicide. *Int J Epidemiol*, **39**(6). 1478-84.

Griffith, J. D., Cavanaugh, J., Held, J. & Oates, J. A. (1972) Dextroamphetamine. Evaluation of psychomimetic properties in man. *Arch Gen Psychiatry*, **26**(2). 97-100.

Griffiths, R. R., Troisi, J. R., Silverman, K. & Mumford, G. K. (1993) Multiple-choice procedure: an efficient approach for investigating drug reinforcement in humans. *Behav Pharmacol*, **4**(1). 3-13.

Grunder, G., Carlsson, A. & Wong, D. F. (2003) Mechanism of new antipsychotic medications: occupancy is not just antagonism. *Arch Gen Psychiatry*, **60**(10). 974-7.

Guy, W. (1976) *ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publ No ADM 76-338)*. Rockville, MD, page 218-222 U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs.

Haile, C. N., Kosten, T. R. & Kosten, T. A. (2009) Pharmacogenetic treatments for drug addiction: cocaine, amphetamine and methamphetamine. *Am J Drug Alcohol Abuse*, **35**(3). 161-77.

Hall, F. S., Drgonova, J., Goeb, M. & Uhl, G. R. (2003) Reduced behavioral effects of cocaine in heterozygous brain-derived neurotrophic factor (BDNF) knockout mice. *Neuropsychopharmacology*, **28**(8). 1485-90.

Hall, W., Hando, J., Darke, S. & Ross, J. (1996) Psychological morbidity and route of administration among amphetamine users in Sydney, Australia. *Addiction*, **91**(1). 81-7.

Hando, J. & Hall, W. (1994) HIV risk-taking behaviour among amphetamine users in Sydney, Australia. *Addiction*, **89**(1). 79-85.

Haro, J. M., Kamath, S. A., Ochoa, S., Novick, D., Rele, K., Fargas, A., Rodriguez, M. J., Rele, R., Orta, J., Kharbeng, A., Araya, S., Gervin, M.,

Bibliography

- Alonso, J., Mavreas, V., Lavrentzou, E., Lontos, N., Gregor, K. & Jones, P. B. (2003) The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta Psychiatr Scand Suppl*, **416**:16-23.
- Hasan, A. A. & Ciancio, S. (2004) Relationship between amphetamine ingestion and gingival enlargement. *Pediatr Dent*, **26**(5). 396-400.
- Henry, J. A., Jeffreys, K. J. & Dawling, S. (1992) Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). *Lancet*, **340**(8816). 384-7.
- Herrmann, C. (1997) International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res*, **42**(1). 17-41.
- Hofer, M., Pagliusi, S. R., Hohn, A., Leibrock, J. & Barde, Y. A. (1990) Regional distribution of brain-derived neurotrophic factor mRNA in the adult mouse brain. *EMBO J*, **9**(8). 2459-64.
- Hofmann, F. (1983) *A handbook on drug and alcohol abuse: the biomedical aspects.*, 2nd ed. New York, Oxford University Press.
- Hoge, E. A., Worthington, J. J., 3rd, Kaufman, R. E., Delong, H. R., Pollack, M. H. & Simon, N. M. (2008) Aripiprazole as augmentation treatment of refractory generalized anxiety disorder and panic disorder. *CNS Spectr*, **13**(6). 522-7.
- Horton, D. K., Berkowitz, Z. & Kaye, W. M. (2003) The acute health consequences to children exposed to hazardous substances used in illicit methamphetamine production, 1996-2001. *J Child Health*, **1**:99-108.
- Huber, C. G., Lambert, M., Naber, D., Schacht, A., Hundemer, H. P., Wagner, T. T. & Schimmelmann, B. G. (2008) Validation of a Clinical Global Impression Scale for Aggression (CGI-A) in a sample of 558 psychiatric patients. *Schizophr Res*, **100**(1-3). 342-8.
- Hunter, R. H., Joy, C. B., Kennedy, E., Gilbody, S. M. & Song, F. (2003) Risperidone versus typical antipsychotic medication for schizophrenia. *Cochrane Database Syst Rev*, (2). CD000440.
- Iqbal, N., Lambert, T. & Masand, P. (2007) Akathisia: problem of history or concern of today. *CNS Spectr*, **12**(9 -14). 1-13.
- Itoh, K., Hashimoto, K., Shimizu, E., Sekine, Y., Ozaki, N., Inada, T., Harano, M., Iwata, N., Komiyama, T., Yamada, M., Sora, I., Nakata, K., Ujike, H. & Iyo, M. (2005) Association study between brain-derived neurotrophic factor gene polymorphisms and methamphetamine abusers in Japan. *Am J Med Genet B Neuropsychiatr Genet*, **132**(1). 70-3.

Bibliography

- Iwanami, A., Kuwakado, D., Otsubo, T., Ishono, H. & Kamijima, K. (1997) Relapse of panic disorder induced by a single intravenous methamphetamine injection. *J Anxiety Disord*, **11**(1). 113-6.
- Iwanami, A., Sugiyama, A., Kuroki, N., Toda, S., Kato, N., Nakatani, Y., Horita, N. & Kaneko, T. (1994) Patients with methamphetamine psychosis admitted to a psychiatric hospital in Japan. A preliminary report. *Acta Psychiatr Scand*, **89**(6). 428-32.
- James, D., Davies, G. & Willner, P. (2004) The development and initial validation of a questionnaire to measure craving for amphetamine. *Addiction*, **99**(9). 1181-8.
- Janno, S., Holi, M. M., Tuisku, K. & Wahlbeck, K. (2005) Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. *BMC Neurol*, **5**(1). 5.
- Jayaram-Lindstrom, N., Konstenius, M., Eksborg, S., Beck, O., Hammarberg, A. & Franck, J. (2008) Naltrexone attenuates the subjective effects of amphetamine in patients with amphetamine dependence. *Neuropsychopharmacology*, **33**(8). 1856-63.
- Jenkinson, R. & Johnston, J. (2006) Methamphetamine use in Melbourne, Australia's drug trend monitoring systems: page 1-5. *Drug Trends Bulletin*. the IDRS and PDI studies.
- Johnson, E. O., Van Den Bree, M. B., Uhl, G. R. & Pickens, R. W. (1996) Indicators of genetic and environmental influences in drug abusing individuals. *Drug Alcohol Depend*, **41**(1). 17-23.
- Johnson, T. D. & Berenson, M. M. (1991) Methamphetamine-induced ischemic colitis. *J Clin Gastroenterol*, **13**(6). 687-9.
- Johnston, M., Pollard, B. & Hennessey, P. (2000) Construct validation of the hospital anxiety and depression scale with clinical populations. *J Psychosom Res*, **48**(6). 579-84.
- Joling, K. J., Van Hout, H. P., Scheltens, P., Vernooij-Dassen, M., Van Den Berg, B., Bosmans, J., Gillissen, F., Mittelman, M. & Van Marwijk, H. W. (2008) (Cost)-effectiveness of family meetings on indicated prevention of anxiety and depressive symptoms and disorders of primary family caregivers of patients with dementia: design of a randomized controlled trial. *BMC Geriatr*, **8**:2.
- Jones, A. L., Jarvie, D. R., Mcdermid, G. & Proudfoot, A. T. (1994) Hepatocellular damage following amphetamine intoxication. *J Toxicol Clin Toxicol*, **32**(4). 435-44.

Bibliography

- Judd, F., Jackson, H., Komiti, A., Bell, R. & Fraser, C. (2010) The profile of suicide: changing or changeable? *Soc Psychiatry Psychiatr Epidemiol*, **41**(2). 20-28.
- Kalechstein, A. D., Newton, T. F., Longshore, D., Anglin, M. D., Van Gorp, W. G. & Gawin, F. H. (2000) Psychiatric comorbidity of methamphetamine dependence in a forensic sample. *J Neuropsychiatry Clin Neurosci*, **12**(4). 480-4.
- Kamijo, Y., Soma, K., Nishida, M., Namera, A. & Ohwada, T. (2002) Acute liver failure following intravenous methamphetamine. *Vet Hum Toxicol*, **44**(4). 216-7.
- Kandel, D. B. & Davies, M. (1986) Adult sequelae of adolescent depressive symptoms. *Arch Gen Psychiatry*, **43**(3). 255-62.
- Kane, J. M., Carson, W. H., Saha, A. R., Mcquade, R. D., Ingenito, G. G., Zimbroff, D. L. & Ali, M. W. (2002) Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*, **63**(9). 763-71.
- Kane, J. M., Fleischhacker, W. W., Hansen, L., Perlis, R., Pikalov, A., 3rd & Assuncao-Talbott, S. (2009) Akathisia: an updated review focusing on second-generation antipsychotics. *J Clin Psychiatry*, **70**(5). 627-43.
- Kapur, S. (2004) How antipsychotics become anti-"psychotic"--from dopamine to salience to psychosis. *Trends Pharmacol Sci*, **25**(8). 402-6.
- Kay-Lambkin, F. J., Baker, A. L., Mcketin, R. & Lee, N. (2010) Stepping through treatment: reflections on an adaptive treatment strategy among methamphetamine users with depression. *Drug Alcohol Rev*, **29**(5). 475-82.
- Kay, S. R., Fiszbein, A. & Opler, L. A. (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*, **13**(2). 261-76.
- Kaye, S., Mcketin, R., Duflou, J. & Darke, S. (2007) Methamphetamine and cardiovascular pathology: a review of the evidence. *Addiction*, **102**(8). 1204-11.
- Kdn (2010) Agensi Antidadah Kebangsaan, Kementerian Dalam Negeri, Malaysia. *Laporan Dadah Mac*.
- Keck, P. E., Jr., Calabrese, J. R., McIntyre, R. S., Mcquade, R. D., Carson, W. H., Eudicone, J. M., Carlson, B. X., Marcus, R. N. & Sanchez, R. (2007) Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *J Clin Psychiatry*, **68**(10). 1480-91.

Bibliography

- Kendler, K. S., Karkowski, L. M., Neale, M. C. & Prescott, C. A. (2000) Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Arch Gen Psychiatry*, **57**(3). 261-9.
- Kendler, K. S., Neale, M. C., Heath, A. C., Kessler, R. C. & Eaves, L. J. (1994) A twin-family study of alcoholism in women. *Am J Psychiatry*, **151**(5). 707-15.
- Kern, R. S., Green, M. F., Cornblatt, B. A., Owen, J. R., McQuade, R. D., Carson, W. H., Ali, M. & Marcus, R. (2006) The neurocognitive effects of aripiprazole: an open-label comparison with olanzapine. *Psychopharmacology (Berl)*, **187**(3). 312-20.
- Kim, C., Jung, S. H., Kang, D. R., Kim, H. C., Moon, K. T., Hur, N. W., Shin, D. C. & Suh, I. (2010a) Ambient particulate matter as a risk factor for suicide. *Am J Psychiatry*, **167**(9). 1100-7.
- Kim, N., Mickelson, J. B., Brenner, B. E., Haws, C. A., Yurgelun-Todd, D. A. & Renshaw, P. F. (2011) Altitude, gun ownership, rural areas, and suicide. *Am J Psychiatry*, **168**(1). 49-54.
- Kim, Y., Kim, H. & Kim, D. S. (2010b) Association between daily environmental temperature and suicide mortality in Korea (2001-2005). *Psychiatry Res*, **67**(3). 67-71.
- Kolecki, P. (1998) Inadvertent methamphetamine poisoning in pediatric patients. *Pediatr Emerg Care*, **14**(6). 385-7.
- Kolotkin, R. L., Corey-Lisle, P. K., Crosby, R. D., Kan, H. J. & McQuade, R. D. (2008) Changes in weight and weight-related quality of life in a multicentre, randomized trial of aripiprazole versus standard of care. *Eur Psychiatry*, **23**(8). 561-6.
- Kosten, T. R. & Singha, A. K. (1999) Stimulants. IN Marc, G. & Kleber, H. D. (Eds.) *Textbook of substance abuse treatment* 2nd ed. Washington DC, American Psychiatric Press.
- Krebs, M. O., Guillin, O., Bourdell, M. C., Schwartz, J. C., Olie, J. P., Poirier, M. F. & Sokoloff, P. (2000) Brain derived neurotrophic factor (BDNF) gene variants association with age at onset and therapeutic response in schizophrenia. *Mol Psychiatry*, **5**(5). 558-62.
- Kurtz, S. P. & Inciardi, J. A. (2003) Crystal meth, gay men and circuit parties. *Law Enforcement Executive Forum*, **3**(4). 97-114.
- Lago, J. A. & Kosten, T. R. (1994) Stimulant withdrawal. *Addiction*, **89**(11). 1477-81.

Bibliography

- Larson, M.(2008) Amphetamine related psychiatric disorders. eMedicine. 29 January 2008 [cited 3 Jan 2011]; Available from: <http://www.emedicine.com/med/topic3114.htm>.
- Le Foll, B., Diaz, J. & Sokoloff, P. (2005) A single cocaine exposure increases BDNF and D3 receptor expression: implications for drug-conditioning. *Neuroreport*, **16**(2). 175-8.
- Leduc, P. A. & Mittleman, G. (1995) Schizophrenia and psychostimulant abuse: a review and re-analysis of clinical evidence. *Psychopharmacology (Berl)*, **121**(4). 407-27.
- Lee, N. E., Taylor, M. M., Bancroft, E., Ruane, P. J., Morgan, M., McCoy, L. & Simon, P. A. (2005) Risk factors for community-associated methicillin-resistant *Staphylococcus aureus* skin infections among HIV-positive men who have sex with men. *Clin Infect Dis*, **40**(10). 1529-34.
- Leelahanaj, T., Kongsakon, R. & Netrakom, P. (2005) A 4-week, double-blind comparison of olanzapine with haloperidol in the treatment of amphetamine psychosis. *J Med Assoc Thai*, **88** (3). S43-52.
- Leite, J. V., Guimaraes, F. S. & Moreira, F. A. (2008) Aripiprazole, an atypical antipsychotic, prevents the motor hyperactivity induced by psychotomimetics and psychostimulants in mice. *Eur J Pharmacol*, **578**(2-3). 222-7.
- Leshner, A. I. (1999) Science-based views of drug addiction and its treatment. *JAMA*, **282**(14). 1314-6.
- Leucht, S., Kane, J. M., Etschel, E., Kissling, W., Hamann, J. & Engel, R. R. (2006) Linking the PANSS, BPRS, and CGI: clinical implications. *Neuropsychopharmacology*, **31**(10). 2318-25.
- Lewman, L. V. (1972) Fatal pulmonary hypertension from intravenous injection of methylphenidate (Ritalin) tablets. *Hum Pathol*, **3**(1). 67-70.
- Li, T., Chen, C. K., Hu, X., Ball, D., Lin, S. K., Chen, W., Sham, P. C., Loh El, W., Murray, R. M. & Collier, D. A. (2004) Association analysis of the DRD4 and COMT genes in methamphetamine abuse. *Am J Med Genet B Neuropsychiatr Genet*, **129**(1). 120-4.
- Li, Y., Rowland, C., Tacey, K., Catanese, J., Sninsky, J., Hardy, J., Powell, J., Lovestone, S., Morris, J. C., Thal, L., Goate, A., Owen, M., Williams, J. & Grupe, A. (2005) The BDNF Val66Met polymorphism is not associated with late onset Alzheimer's disease in three case-control samples. *Mol Psychiatry*, **10**(9). 809-10.

Bibliography

- Lieberman, J. A. (2004) Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs*, **18**(4). 251-67.
- Lile, J. A., Stoops, W. W., Vansickel, A. R., Glaser, P. E., Hays, L. R. & Rush, C. R. (2005) Aripiprazole attenuates the discriminative-stimulus and subject-rated effects of D-amphetamine in humans. *Neuropsychopharmacology*, **30**(11). 2103-14.
- Linszen, D. H., Dingemans, P. M. & Lenior, M. E. (1994) Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiatry*, **51**(4). 273-9.
- Liu, Q. R., Walther, D., Drgon, T., Polesskaya, O., Lesnick, T. G., Strain, K. J., De Andrade, M., Bower, J. H., Maraganore, D. M. & Uhl, G. R. (2005) Human brain derived neurotrophic factor (BDNF) genes, splicing patterns, and assessments of associations with substance abuse and Parkinson's Disease. *Am J Med Genet B Neuropsychiatr Genet*, **134**(1). 93-103.
- Longo, M., Wickes, W., Smout, M., Harrison, S., Cahill, S. & White, J. M. Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. *Addiction*, **105**(1). 146-54.
- Lopez-Meza, E., Ruiz-Chow, A. & Ramirez-Bermudez, J. (2005) Aripiprazole in psychosis associated with Parkinson's disease. *J Neuropsychiatry Clin Neurosci*, **17**(3). 421-2.
- Luthar, S. S. & Rounsaville, B. J. (1993) Substance misuse and comorbid psychopathology in a high-risk group: a study of siblings of cocaine misusers. *Int J Addict*, **28**(5). 415-34.
- Marcus, R. N., Mcquade, R. D., Carson, W. H., Hennicken, D., Fava, M., Simon, J. S., Trivedi, M. H., Thase, M. E. & Berman, R. M. (2008) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*, **28**(2). 156-65.
- Marder, S. R., Mcquade, R. D., Stock, E., Kaplita, S., Marcus, R., Safferman, A. Z., Saha, A., Ali, M. & Iwamoto, T. (2003) Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res*, **61**(2-3). 123-36.
- Markou, A. & Kenny, P. J. (2002) Neuroadaptations to chronic exposure to drugs of abuse: relevance to depressive symptomatology seen across psychiatric diagnostic categories. *Neurotox Res*, **4**(4). 297-313.
- Marshall, B. D., Wood, E., Shoveller, J. A., Patterson, T. L., Montaner, J. S. & Kerr, T. (2011) Pathways to HIV risk and vulnerability among lesbian, gay,

Bibliography

bisexual, and transgendered methamphetamine users: a multi-cohort gender-based analysis. *BMC Public Health*, **11**:20-29.

Mau, M. K., Asao, K., Efird, J., Saito, E., Ratner, R., Hafi, M. & Seto, T. (2009) Risk factors associated with methamphetamine use and heart failure among native Hawaiians and other Pacific Island peoples. *Vasc Health Risk Manag*, **5**(1). 45-52.

Maxwell, J. C. (2005) Emerging research on methamphetamine. *Curr Opin Psychiatry*, **18**(3). 235-42.

Mcgregor, C., Srisurapanont, M., Jittiwutikarn, J., Laobhripatr, S., Wongtan, T. & White, J. M. (2005) The nature, time course and severity of methamphetamine withdrawal. *Addiction*, **100**(9). 1320-9.

Mcketin, R., Kelly, E. & McLaren, J. (2006a) The relationship between crystalline methamphetamine use and methamphetamine dependence. *Drug Alcohol Depend*, **85**(3). 198-204.

Mcketin, R., McLaren, J. & Kelly, E. (2005) *The Sydney methamphetamine market: patters of supply, use, personal harms and social consequences*, Monograph series no. 13 (National Drug Law Enforcement Research Fund, Australia)

Mcketin, R., McLaren, J., Lubman, D. I. & Hides, L. (2006b) The prevalence of psychotic symptoms among methamphetamine users. *Addiction*, **101**(10). 1473-8.

Mcquade, R. D., Stock, E., Marcus, R., Jody, D., Gharbia, N. A., Vanveggel, S., Archibald, D. & Carson, W. H. (2004) A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry*, **65** (18). 47-56.

Meredith, C. W., Jaffe, C., Yanasak, E., Cherrier, M. & Saxon, A. J. (2007) An open-label pilot study of risperidone in the treatment of methamphetamine dependence. *J Psychoactive Drugs*, **39**(2). 167-72.

Miles, D. R., Van Den Bree, M. B., Gupman, A. E., Newlin, D. B., Glantz, M. D. & Pickens, R. W. (2001) A twin study on sensation seeking, risk taking behavior and marijuana use. *Drug Alcohol Depend*, **62**(1). 57-68.

Mirin, S. M., Weiss, R. D., Griffin, M. L. & Michael, J. L. (1991) Psychopathology in drug abusers and their families. *Compr Psychiatry*, **32**(1). 36-51.

Misra, L. & Kofoed, L. (1997) Risperidone treatment of methamphetamine psychosis. *Am J Psychiatry*, **154**(8). 1170.

Bibliography

- Misra, L. K., Kofoed, L., Oesterheld, J. R. & Richards, G. A. (2000) Olanzapine treatment of methamphetamine psychosis. *J Clin Psychopharmacol*, **20**(3). 393-4.
- Mmwr (2006) Methamphetamine use and HIV risk behaviors among heterosexual men--preliminary results from five northern California counties, December 2001-November 2003. *MMWR Morb Mortal Wkly Rep*, **55**(10). 273-7.
- Moorey, S., Greer, S., Watson, M., Gorman, C., Rowden, L., Tunmore, R., Robertson, B. & Bliss, J. (1991) The factor structure and factor stability of the hospital anxiety and depression scale in patients with cancer. *Br J Psychiatry*, **158**:255-9.
- Murphy, D. L., Lerner, A., Rudnick, G. & Lesch, K. P. (2004) Serotonin transporter: gene, genetic disorders, and pharmacogenetics. *Mol Interv*, **4**(2). 109-23.
- Mykletun, A., Stordal, E. & Dahl, A. A. (2001) Hospital Anxiety and Depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. *Br J Psychiatry*, **179**:540-4.
- Nakamura, K., Chen, C. K., Sekine, Y., Iwata, Y., Anitha, A., Loh El, W., Takei, N., Suzuki, A., Kawai, M., Takebayashi, K., Suzuki, K., Minabe, Y., Tsuchiya, K., Yamada, K., Iyo, M., Ozaki, N., Inada, T., Iwata, N., Harano, M., Komiyama, T., Yamada, M., Sora, I., Ujike, H., Ball, D. M., Yoshikawa, T., Lin, S. K. & Mori, N. (2006) Association analysis of SOD2 variants with methamphetamine psychosis in Japanese and Taiwanese populations. *Hum Genet*, **120**(2). 243-52.
- Ndcp.(2007) Drug facts: methamphetamine. Office of National Drug Control Policy. [cited 22 January 2011]; Available from: <http://www.whitehousedrugpolicy.gov/drugfact/methamphetamine/index.html>.
- Nestler, E. J. (2000) Genes and addiction. *Nat Genet*, **26**(3). 277-81.
- Newton, T. F., Reid, M. S., De La Garza, R., Mahoney, J. J., Abad, A., Condos, R., Palamar, J., Halkitis, P. N., Mojisak, J., Anderson, A., Li, S. H. & Elkashef, A. (2008) Evaluation of subjective effects of aripiprazole and methamphetamine in methamphetamine-dependent volunteers. *Int J Neuropsychopharmacol*, **11**(8). 1037-45.
- Newton, T. F., Roache, J. D., De La Garza, R., 2nd, Fong, T., Wallace, C. L., Li, S. H., Elkashef, A., Chiang, N. & Kahn, R. (2006) Bupropion reduces methamphetamine-induced subjective effects and cue-induced craving. *Neuropsychopharmacology*, **31**(7). 1537-44.

Bibliography

Nhduh.(2005) Methamphetamine use, abuse, and dependence: 2002,2003 and 2004.NHDUH Report, 16 September 2005. [cited 2 February 2011]; Available from:

<http://www.drugabusestatistics.samhsa.gov/2k5/meth/meth.htm>.

Nida (1998) *Methamphetamine: abuse and addiction* (NIH Publication No.98-4210), National Institute on Drug Abuse.Washington DC.

Nst.(2010) Malaysia drug-free by 2015. New Straits Times; 12 Feb [cited 15 January, 2011]; Available from: http://findarticles.com/p/news-articles/new-straits-times/mi_8016/is_20100212/malaysia-drug-free-2015/ai_n49495484.

O'malley, S. S., Jaffe, A. J., Chang, G., Schottenfeld, R. S., Meyer, R. E. & Rounsaville, B. (1992) Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Arch Gen Psychiatry*, **49(11)**. 881-7.

Oro, A. S. & Dixon, S. D. (1987) Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. *J Pediatr*, **111(4)**. 571-8.

Parker, E. M. & Cubeddu, L. X. (1986) Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. *J Pharmacol Exp Ther*, **237(1)**. 179-92.

Peck, J. A., Reback, C. J., Yang, X., Rotheram-Fuller, E. & Shoptaw, S. (2005) Sustained reductions in drug use and depression symptoms from treatment for drug abuse in methamphetamine-dependent gay and bisexual men. *J Urban Health*, **82(1)** . i100-8.

Pemadam.(2011) Akta & Undang-Undang Dadah. [cited 15 February 2011]; Available from: http://www.pemadam.org.my/cda/m_fakta/fkt_akta_main.php.

Perez, J. A., Jr., Arsura, E. L. & Strategos, S. (1999) Methamphetamine-related stroke: four cases. *J Emerg Med*, **17(3)**. 469-71.

Pickens, R. W., Svikis, D. S., Mcgue, M. & Labuda, M. C. (1995) Common genetic mechanisms in alcohol, drug, and mental disorder comorbidity. *Drug Alcohol Depend*, **39(2)**. 129-38.

Poling, J., Oliveto, A., Petry, N., Sofuoglu, M., Gonsai, K., Gonzalez, G., Martell, B. & Kosten, T. R. (2006) Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Arch Gen Psychiatry*, **63(2)**. 219-28.

Poudel-Tandukar, K., Nanri, A., Mizoue, T., Matsushita, Y., Takahashi, Y., Noda, M., Inoue, M. & Tsugane, S. (2010) Differences in suicide risk according to living arrangements in Japanese men and women - The Japan

Bibliography

Public Health Center-based (JPHC) prospective study. *J Affect Disord*, **34(9)**. 256-264.

Pregelj, P., Nedic, G., Paska, A. V., Zupanc, T., Nikolac, M., Balazic, J., Tomori, M., Komel, R., Seler, D. M. & Pivac, N. (2011) The association between brain-derived neurotrophic factor polymorphism (BDNF Val66Met) and suicide. *J Affect Disord*, **128(3)**. 287-90.

Pulvirenti, L. & Koob, G. F. (2002) Being partial to psychostimulant addiction therapy. *Trends Pharmacol Sci*, **23(4)**. 151-3.

Quest-Diagnostics.(2003) Increased use of amphetamines linked to rising workplace drug use,according to Quest Diagnostics' 2003 Drug Testing Index .[cited 8 November 2010]; Available from:
http://www.questdiagnostics.com/employersolutions/dti_07_2004/dti_index.html. .

Rawson, R. A., Gonzales, R. & Brethen, P. (2002a) Treatment of methamphetamine use disorders: an update. *J Subst Abuse Treat*, **23(2)**. 145-50.

Rawson, R. A., Huber, A., Mccann, M., Shoptaw, S., Farabee, D., Reiber, C. & Ling, W. (2002b) A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance treatment for cocaine dependence. *Arch Gen Psychiatry*, **59(9)**. 817-24.

Rawson, R. A., Marinelli-Casey, P., Anglin, M. D., Dickow, A., Frazier, Y., Gallagher, C., Galloway, G. P., Herrell, J., Huber, A., Mccann, M. J., Obert, J., Pennell, S., Reiber, C., Vandersloot, D. & Zweben, J. (2004) A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. *Addiction*, **99(6)**. 708-17.

Reback, C. J., Larkins, S. & Shoptaw, S. (2004) Changes in the meaning of sexual risk behaviors among gay and bisexual male methamphetamine abusers before and after drug treatment. *AIDS Behav*, **8(1)**. 87-98.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L. & Goodwin, F. K. (1990) Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*, **264(19)**. 2511-8.

Rhodus, N. L. & Little, J. W. (2005) Methamphetamine abuse and "meth mouth". *Northwest Dent*, **84(5)**. 29, 31, 33-7.

Richards, J. R., Derlet, R. W. & Albertson, T. E.(2009) Toxicity, methamphetamine. eMedicine. [cited 22 November 2010]; Available from:
<http://www.emedicine.com/EMERG/topic859.htm#section~introduction>.

Bibliography

- Richards, J. R., Derlet, R. W. & Duncan, D. R. (1998) Chemical restraint for the agitated patient in the emergency department: lorazepam versus droperidol. *J Emerg Med*, **16**(4). 567-73.
- Rounsaville, B. J., Kosten, T. R., Weissman, M. M., Prusoff, B., Pauls, D., Anton, S. F. & Merikangas, K. (1991) Psychiatric disorders in relatives of probands with opiate addiction. *Arch Gen Psychiatry*, **48**(1). 33-42.
- Rush, J. A. (2000) Abnormal Involuntary Movement Scale (AIMS). in *Handbook of Psychiatric Measures*. page 166-168 American Psychiatric Association.
- Rutter, J. L. (2006) Symbiotic relationship of pharmacogenetics and drugs of abuse. *The American Association of Pharmaceutical Scientists Journal*, **8**(1). E174-84.
- Salo, R., Nordahl, T. E., Leamon, M. H., Natsuaki, Y., Moore, C. D., Waters, C. & Carter, C. S. (2008) Preliminary evidence of behavioral predictors of recurrent drug-induced psychosis in methamphetamine abuse. *Psychiatry Res*, **157**(1-3). 273-7.
- Sato, M. (1992) A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. *Ann N Y Acad Sci*, **654**:160-70.
- Savard, J., Laberge, B., Gauthier, J. G., Ivers, H. & Bergeron, M. G. (1998) Evaluating anxiety and depression in HIV-infected patients. *J Pers Assess*, **71**(3). 349-67.
- Schwabe, K. & Koch, M. (2007) Effects of aripiprazole on operant responding for a natural reward after psychostimulant withdrawal in rats. *Psychopharmacology (Berl)*, **191**(3). 759-65.
- Sekine, Y., Minabe, Y., Ouchi, Y., Takei, N., Iyo, M., Nakamura, K., Suzuki, K., Tsukada, H., Okada, H., Yoshikawa, E., Futatsubashi, M. & Mori, N. (2003) Association of dopamine transporter loss in the orbitofrontal and dorsolateral prefrontal cortices with methamphetamine-related psychiatric symptoms. *Am J Psychiatry*, **160**(9). 1699-701.
- Sellers, E. M. & Tyndale, R. F. (2000) Mimicking gene defects to treat drug dependence. *Ann N Y Acad Sci*, **909**:233-46.
- Semple, S. J., Patterson, T. L. & Grant, I. (2004) The context of sexual risk behavior among heterosexual methamphetamine users. *Addict Behav*, **29**(4). 807-10.
- Shearer, J., Darke, S., Rodgers, C., Slade, T., Van Beek, I., Lewis, J., Brady, D., Mcketin, R., Mattick, R. P. & Wodak, A. (2009) A double-blind, placebo-

Bibliography

controlled trial of modafinil (200 mg/day) for methamphetamine dependence. *Addiction*, **104**(2). 224-33.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E. & Al., E. (1998a) *The Mini-International Neuropsychiatric Interview (M.I.N.I.):5.0.0. Malay version/DSM-IV/current*, University of South Florida-TAMPA,USA.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R. & Dunbar, G. C. (1998b) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*, **59** (20). 22-33;quiz 34-57.

Shoptaw, S. (2006) Methamphetamine use in urban gay and bisexual populations. *Top HIV Med*, **14**(2). 84-7.

Shoptaw, S., Heinzerling, K. G., Rotheram-Fuller, E., Steward, T., Wang, J., Swanson, A. N., De La Garza, R., Newton, T. & Ling, W. (2008) Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. *Drug Alcohol Depend*, **96**(3). 222-32.

Shoptaw, S., Huber, A., Peck, J., Yang, X., Liu, J., Jeff, D., Roll, J., Shapiro, B., Rotheram-Fuller, E. & Ling, W. (2006) Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug Alcohol Depend*, **85**(1). 12-8.

Shoptaw, S., Peck, J., Reback, C. J. & Rotheram-Fuller, E. (2003) Psychiatric and substance dependence comorbidities, sexually transmitted diseases, and risk behaviors among methamphetamine-dependent gay and bisexual men seeking outpatient drug abuse treatment. *J Psychoactive Drugs*, **35** (1). 161-8.

Shoptaw, S., Rawson, R. A., Mccann, M. J. & Obert, J. L. (1994) The Matrix model of outpatient stimulant abuse treatment: evidence of efficacy. *J Addict Dis*, **13**(4). 129-41.

Shoptaw, S., Reback, C. J. & Freese, T. E. (2002) Patient characteristics, HIV serostatus, and risk behaviors among gay and bisexual males seeking treatment for methamphetamine abuse and dependence in Los Angeles. *J Addict Dis*, **21**(1). 91-105.

Shoptaw, S., Reback, C. J., Peck, J. A., Yang, X., Rotheram-Fuller, E., Larkins, S., Veniegas, R. C., Freese, T. E. & Hucks-Ortiz, C. (2005) Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend*, **78**(2). 125-34.

Bibliography

Simpson, G. M. & Angus, J. W. (1970) A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl*, **212**:11-9.

Singhanetra-Renard, A. (1993) Socio-economic and political impact for production, trade and use of narcotic drugs in Thailand. *UNRISD and the United Nations University*, 87.

Sipe, J. C., Chiang, K., Gerber, A. L., Beutler, E. & Cravatt, B. F. (2002) A missense mutation in human fatty acid amide hydrolase associated with problem drug use. *Proc Natl Acad Sci U S A*, **99**(12). 8394-9.

Smith, L., Yonekura, M. L., Wallace, T., Berman, N., Kuo, J. & Berkowitz, C. (2003) Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. *J Dev Behav Pediatr*, **24**(1). 17-23.

Somoza E, B. S., Himmler C, Et Al (1999a) The Brief Substance Craving Scale—measuring craving in clinical trials. *NIDA Res Monogr.*, **180**:304.

Somoza E, B. S., Himmler C, Et Al (1999b) The Brief Substance Craving Scale—measuring craving in clinical trials. *NIDA Res Monogr.*, **180**:304.

Srisurapanont, M., Ali, R., Marsden, J., Sunga, A., Wada, K. & Monteiro, M. (2003) Psychotic symptoms in methamphetamine psychotic in-patients. *Int J Neuropsychopharmacol*, **6**(4). 347-52.

Srisurapanont, M., Jarusuraisin, N. & Kittirattanapaiboon, P. (2001a) Treatment for amphetamine dependence and abuse. *Cochrane Database Syst Rev*, (4). CD003022.

Srisurapanont, M., Kittirattanapaiboon, P. & Jarusuraisin, N. (2001b) Treatment for amphetamine psychosis. *Cochrane Database Syst Rev*, (4). CD003026.

Srisurapanont, M., Maneeton, B. & Maneeton, N. (2004) Quetiapine for schizophrenia. *Cochrane Database Syst Rev*, (2). CD000967.

Stahl, S. M. (2001) Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part 1, "Goldilocks" actions at dopamine receptors. *J Clin Psychiatry*, **62**(11). 841-2.

Star.(2007) 123 kg of syabu seized, RM5.8 million cash recovered.The Star,10 April 2007. [cited 12 December 2010]; Available from:
<http://www.thestar.com.my/news/story.asp?file=/2007/4/10/nation/17392866&sec=nation>.

Bibliography

- Stein, D. J., Westenberg, H. G. & Liebowitz, M. R. (2002) Social anxiety disorder and generalized anxiety disorder: serotonergic and dopaminergic neurocircuitry. *J Clin Psychiatry*, **63** (6). 12-9.
- Stewart, J. L. & Meeker, J. E. (1997) Fetal and infant deaths associated with maternal methamphetamine abuse. *J Anal Toxicol*, **21**(6). 515-7.
- Stoops, W. W. (2006) Aripiprazole as a potential pharmacotherapy for stimulant dependence: human laboratory studies with d-amphetamine. *Exp Clin Psychopharmacol*, **14**(4). 413-21.
- Stoops, W. W., Lile, J. A., Glaser, P. E. & Rush, C. R. (2006) A low dose of aripiprazole attenuates the subject-rated effects of d-amphetamine. *Drug Alcohol Depend*, **84**(2). 206-9.
- Strakowski, S. M. & Delbello, M. P. (2000) The co-occurrence of bipolar and substance use disorders. *Clin Psychol Rev*, **20**(2). 191-206.
- Strange, P. G. (2001) Antipsychotic drugs: importance of dopamine receptors for mechanisms of therapeutic actions and side effects. *Pharmacol Rev*, **53**(1). 119-33.
- Suwaki H., Fukui S. & Konuma K. (2007) Amphetamine Misuse: International Perspective on Current Trends. IN Klee, H. (Ed.) *In: Methamphetamine abuse in Japan: its 45-years history and the current situation* .page 199-214.Harwood Academic: Amsterdam.
- Swanson, J., Baler, R. D. & Volkow, N. D. (2010) Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. *Neuropsychopharmacology*, **36**(1). 207-26.
- Swendsen, J., Conway, K. P., Degenhardt, L., Glantz, M., Jin, R., Merikangas, K. R., Sampson, N. & Kessler, R. C. (2010) Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey. *Addiction*, **105**(6). 1117-28.
- Swetlow, K.(2003) US Department of Justice. Children at Clandestine Methamphetamine Labs:Helping Meth's Youngest Victims. OVC Bulletin June 2003. [cited 3 February 2011]; Available from: <http://www.ojp.usdoj.gov/ovc/publications/bulletins/children/197590.pdf>.
- Swofford, C. D., Kasckow, J. W., Scheller-Gilkey, G. & Inderbitzin, L. B. (1996) Substance use: a powerful predictor of relapse in schizophrenia. *Schizophr Res*, **20**(1-2). 145-151.
- Taylor, D. M. (2003) Aripiprazole: a review of its pharmacology and clinical use. *Int J Clin Pract*, **57**(1). 49-54.

Bibliography

Tempo.(1986) Hukum gantung bagi pendadah,Tempo Online [cited 3 January 2011]; Available from:

<http://majalah.tempointeraktif.com/id/arsip/1986/06/28/LN/mbm.19860628.LN33590.id.html>.

Tiihonen, J., Kuoppasalmi, K., Fohr, J., Tuomola, P., Kuikanmaki, O., Vorma, H., Sokero, P., Haukka, J. & Meririnne, E. (2007) A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *Am J Psychiatry*, **164**(1). 160-2.

Torrent (2003) Prescribing Information:Arip MT(Aripiprazole Tablets).Torrent Pharmaceuticals LTD.Indrad-383 721,Dist. Meahsana,INDIA.

Tsuang, M. T., Lyons, M. J., Eisen, S. A., Goldberg, J., True, W., Lin, N., Meyer, J. M., Toomey, R., Faraone, S. V. & Eaves, L. (1996) Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. *Am J Med Genet*, **67**(5). 473-7.

Tsuang, M. T., Lyons, M. J., Meyer, J. M., Doyle, T., Eisen, S. A., Goldberg, J., True, W., Lin, N., Toomey, R. & Eaves, L. (1998) Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry*, **55**(11). 967-72.

Unodc.(1998a) United Nations Office of Drugs and Crime.Economic and social consequences of drug abuse and illicit trafficking;(No: 6).Vienna, Austria [cited 2 February 2011]; Available from:
http://www.unodc.org/pdf/technical_series_1998-01-01_1.pdf.

Unodc (1998b) United Nations Office on Drugs and Crime. *Economic and social consequences of drug abuse and illicit trafficking:Technical Series No. 6* .Vienna, Austria.

Unodc (2009a) United Nations Office of Drugs and Crime. *World Drug Report* .Vienna, Austria.

Unodc.(2009b) United Nations Office of Drugs and Crime. ATS trends: National trends,Malaysia. Asia & Pacific Amphetamine-type Stimulants Information Centre. . [cited 16 November, 2010]; Available from:
http://www.apaic.org/index.php?option=com_content&view=article&id=130&Itemid=138.

Unodc.(2009c) United Nations Office of Drugs and Crime. ATS trends: regional trends. Asia & Pacific Amphetamine-type Stimulants Information Centre. [cited 16 November, 2010]; Available from:
http://www.apaic.org/index.php?option=com_content&view=article&id=51&Itemid=67

Bibliography

Unodc.(2009d) United Nations Office of Drugs and Crime.ATS information: Effects of ATS Abuse .Asia & Pacific Amphetamine-type Stimulants Information Centre. [cited 2 December 2010]; Available from: http://www.apaic.org/index.php?option=com_content&view=article&id=71&Itemid=86.

Unodc.(2009e) United Nations Office of Drugs and Crime.ATS information: Form of ATS.Asia & Pacific Amphetamine-type Stimulants Information Centre. [cited 24 November 2010]; Available from: http://www.apaic.org/index.php?option=com_content&view=article&id=65&Itemid=80.

Unodc.(2009f) United Nations Office of Drugs and Crime.ATS information: Illicit manufacture. Asia & Pacific Amphetamine-type Stimulants Information Centre. [cited 2 December 2010]; Available from: http://www.apaic.org/index.php?option=com_content&view=article&id=69&Itemid=84.

Unodc.(2011) United Nation Office of Drugs and Crime(UNODC):Legal Tools [cited 14 January 2011]; Available from: <http://www.unodc.org/unodc/en/treaties/index.html?ref=menuaside>.

Urbina, A. & Jones, K. (2004) Crystal methamphetamine, its analogues, and HIV infection: medical and psychiatric aspects of a new epidemic. *Clin Infect Dis*, **38**(6). 890-4.

Utusan.(2006) Harga Perangi Dadah. Utusan Malaysia [cited 2 December 2010]; Available from: http://pendamai.org.my/services/serv_archieve3.php.

Van't Veer-Tazelaar, P. J., Van Marwijk, H. W., Van Oppen, P., Van Hout, H. P., Van Der Horst, H. E., Cuijpers, P., Smit, F. & Beekman, A. T. (2009) Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. *Arch Gen Psychiatry*, **66**(3). 297-304.

Van Kampen, J. & Katz, M. (2001) Persistent psychosis after a single ingestion of 'ecstasy'. *Psychosomatics*, **42**(6). 525-7.

Vocci, F. J. & Appel, N. M. (2007) Approaches to the development of medications for the treatment of methamphetamine dependence. *Addiction*, **102** (1). 96-106.

Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Leonido-Yee, M., Franceschi, D., Sedler, M. J., Gatley, S. J., Hitzemann, R., Ding, Y. S., Logan, J., Wong, C. & Miller, E. N. (2001) Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry*, **158**(3). 377-82.

Bibliography

- Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., Wong, C., Hitzemann, R. & Pappas, N. R. (1999) Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. *J Pharmacol Exp Ther*, **291**(1). 409-15.
- Wagner, F. A. & Anthony, J. C. (2002) From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology*, **26**(4). 479-88.
- Warden, D. L., Gordon, B., Mcallister, T. W. & Al., E. (2006) Neurobehavioral Guidelines Working Group Members: Guidelines for the Pharmacologic Treatment of Neurobehavioral Sequelae of Traumatic Brain Injury *J Neurotrauma*, **23**(10). 1468-1501.
- Weiss, F., Markou, A., Lorang, M. T. & Koob, G. F. (1992) Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. *Brain Res*, **593**(2). 314-8.
- White, F. J. (2002) A behavioral/systems approach to the neuroscience of drug addiction. *J Neurosci*, **22**(9). 3303-5.
- Who (1997) Amphetamine-type stimulants *A report from the WHO meeting on amphetamine, MDMA and other psychostimulants*, Geneva.
- Who.(2011) Management of Substance Abuse:Amphetamine Type Stimulants. [cited 16 February,2011]; Available from:
http://www.who.int/substance_abuse/facts/ATS/en/index.html.
- Wilkins, C., Reilly, J., Rose, E., Roy, D., Pledger, M. & Lee, A. (2004) *The socio-economic impact of amphetamine type stimulants in New Zealand: Final Report.* , Centre for Social and Health Outcomes Research and Evaluation, Massey University, Auckland.
- Wilson, M., Yonette F., Frederick S., Bridget F. (2007) Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*, **64**(5). 566-576.
- Winslow, B. T., Voorhees, K. I. & Pehl, K. A. (2007) Methamphetamine abuse. *Am Fam Physician*, **76**(8). 1169-74.
- Wong, P. W., Chan, W. S., Conwell, Y., Conner, K. R. & Yip, P. S. (2010) A psychological autopsy study of pathological gamblers who died by suicide. *J Affect Disord*, **120**(1-3). 213-6.

Bibliography

- Woody, G. E., Luborsky, L., McLellan, A. T., O'Brien, C. P., Beck, A. T., Blaine, J., Herman, I. & Hole, A. (1983) Psychotherapy for opiate addicts. *NIDA Res Monogr*, **43**:59-70.
- Wouldes, T., Lagasse, L., Sheridan, J. & Lester, B. (2004) Maternal methamphetamine use during pregnancy and child outcome: what do we know? *N Z Med J*, **117**(1206). U1180.
- Wyder, M., Ward, P. & De Leo, D. (2009) Separation as a suicide risk factor. *J Affect Disord*, **116**(3). 208-13.
- Yamada, H., Ishii, Y. & Oguri, K. (2005) Metabolism of Drugs of Abuse: Its Contribution to the Toxicity and the Inter-Individual Differences in Drug Sensitivity. *J. Health Sci.*, **51**(1). 1-7.
- Yamamura, T., Hishida, S., Hatake, K., Taniguchi, T. & Ouchi, H. (1992) Effects of methamphetamine and ethanol on learning and brain neurotransmitters in rats. *Pharmacol Biochem Behav*, **42**(3). 389-400.
- Yamamura, T., Hisida, S. & Hatake, K. (1991) Alcohol addiction of methamphetamine abusers in Japan. *J Forensic Sci*, **36**(3). 754-64.
- Yen, C. F. & Chong, M. Y. (2006) Comorbid psychiatric disorders, sex, and methamphetamine use in adolescents: a case-control study. *Compr Psychiatry*, **47**(3). 215-20.
- Yen, C. F. & Shieh, B. L. (2005) Suicidal ideation and correlates in Taiwanese adolescent methamphetamine users. *J Nerv Ment Dis*, **193**(7). 444-9.
- Yokoi, F., Grunder, G., Biziere, K., Stephane, M., Dogan, A. S., Dannals, R. F., Ravert, H., Suri, A., Bramer, S. & Wong, D. F. (2002) Dopamine D2 and D3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC 14597): a study using positron emission tomography and [¹¹C]raclopride. *Neuropsychopharmacology*, **27**(2). 248-59.
- Yui, K., Goto, K. & Ikemoto, S. (2004) The role of noradrenergic and dopaminergic hyperactivity in the development of spontaneous recurrence of methamphetamine psychosis and susceptibility to episode recurrence. *Ann N Y Acad Sci*, **1025**:296-306.
- Yui, K., Goto, K., Ikemoto, S. & Ishiguro, T. (2000) Stress induced spontaneous recurrence of methamphetamine psychosis: the relation between stressful experiences and sensitivity to stress. *Drug Alcohol Depend*, **58**(1-2). 67-75.
- Yui, K., Goto, K., Ishiguro, T. & Ikemoto, S. (1997) Noradrenergic activity and spontaneous recurrence of methamphetamine psychosis. *Drug Alcohol Depend*, **44**(2-3). 183-7.

Bibliography

Zigmond, A. S. & Snaith, R. P. (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand*, **67**(6). 361-70.

Zimmet, S. V., Strous, R. D., Burgess, E. S., Kohnstamm, S. & Green, A. I. (2000) Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. *J Clin Psychopharmacol*, **20**(1). 94-8.

Zweben, J. E., Cohen, J. B., Christian, D., Galloway, G. P., Salinardi, M., Parent, D. & Iguchi, M. (2004) Psychiatric symptoms in methamphetamine users. *Am J Addict*, **13**(2). 181-90.